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Lob2 ① Nervous system depressants ② Nervous System stimulants ③ Local anesthetics ④ Drugs ⑤ autonomic effector Cells ⑥ water ⑦ salts ⑧ ions ⑨ Gases ⑩ vapors ⑪ heavy metals ⑫ metalloids ⑬ antiseptics ⑭ disinfectants ⑮ Chemotherapy ⑯ hormones ⑰ vitamins

⑱ prescription writing

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The PHARMACOLOGICAL BASIS *of* THERAPEUTICS

A Textbook of Pharmacology, Toxicology and Therapeutics for Physicians and Medical Students

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by

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PREFACE

Three objectives have guided the writing of this book—the correlation of pharmacology with related medical sciences, the reinterpretation of the actions and uses of drugs from the viewpoint of important advances in medicine, and the placing of emphasis on the applications of pharmacodynamics to therapeutics.

Although pharmacology is a basic medical science in its own right, it borrows freely from and contributes generously to the subject matter and technics of many medical disciplines, clinical as well as preclinical. Therefore, the correlation of strictly pharmacological information with medicine as a whole is essential for a proper presentation of pharmacology to students and physicians. Furthermore, the reinterpretation of the actions and uses of well-established therapeutic agents in the light of recent advances in the medical sciences is as important a function of a modern text book of pharmacology as is the description of new drugs. In many instances these new interpretations necessitate radical departures from accepted but outworn concepts of the actions of drugs. Lastly, the emphasis throughout the book, as indicated in its title, has been clinical. This is mandatory because medical students must be taught pharmacology from the standpoint of the actions and uses of drugs in the prevention and treatment of disease. To the student, pharmacological data *per se* are valueless unless he is able to apply his information in the practice of medicine. This book has also been written for the practicing physician, to whom it offers an opportunity to keep abreast of recent advances in therapeutics and to acquire the basic principles necessary for the rational use of drugs in his daily practice.

The criteria for the selection of bibliographic references require comment. It is obviously unwise if not impossible to document every fact included in the text. Preference has therefore been given to articles of a review nature, to the literature on new drugs, and to original contributions in controversial fields. In most instances, only the more recent investigations have been cited. In order to encourage free use of the bibliography, references are chiefly to the available literature in the English language.

The authors are greatly indebted to their many colleagues at the Yale University School of Medicine for their generous help and criticism. In particular they are deeply grateful to Professor Henry Gray Barbour whose constant encouragement and advice have been invaluable.

Louis Goodman
Alfred Gilman

New Haven, Connecticut
November 20, 1940

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The PHARMACOLOGICAL BASIS *of* THERAPEUTICS

SECTION I

INTRODUCTION

CHAPTER 1

GENERAL PRINCIPLES

SCOPE OF PHARMACOLOGY

The subject of pharmacology is a broad one and embraces the knowledge of the source, physical and chemical properties, compounding, physiological actions, absorption, fate and excretion, and therapeutic uses of drugs. A *drug* may be broadly defined as any chemical agent which affects living protoplasm, and few substances would escape inclusion by this definition.

For the medical student and physician, however, the scope of pharmacology and the number of substances to be regarded as drugs are more restricted than indicated by the above definition. The physician is concerned with actions and uses of drugs in the therapy of disease. Obviously his attention is directed toward channels different from those of the pharmacist who compounds drugs, the chemist who synthesizes new medicinals or the botanist who studies the mechanisms by which plants form potent therapeutic agents. Therefore, the study of pharmacology should be approached with specific aims in mind. Before individual drugs are discussed it is fitting to consider the component parts of pharmacology in order to appreciate how best to approach the subject from the standpoint of the interests and requirements of the medical student and practitioner.

The subject of pharmacology in its entirety may be divided into pharmacognosy, pharmacy, pharmacodynamics, pharmacotherapeutics and toxicology.

Pharmacognosy is that branch of pharmacology which deals with the physical characteristics of crude drugs. It is purely a descriptive science. Inasmuch as most crude drugs are of plant origin, pharmacognosy deals largely with the botanical sources of drugs and the characteristics of the plants from which they are obtained. The interests of the physician in pharmacognosy are limited. At one time it was essential for a member of the medical profession to have a broad botanical knowledge, for it was then within his province to select the proper plants and to make from them crude drug preparations. If William Withering had not possessed training in botany, the introduction of digitalis into medicine might have been long delayed. Fortunately, the physician today is not confronted with the problems of pharmacognosy. For him, the drugs of the world are gathered, manufactured and marketed in forms which permit economy, stability, uniformity and ease of administration. However, scientific curiosity should stimulate the physician to gain some conception of the sources of the medicinals which he employs, and often this knowledge proves both interesting and helpful.

Pharmacy deals with the art of preparing, compounding and dispensing medicines. This work at one time lay within the province of the physician, but now it is relegated almost completely to the pharmacist. However, the physician must have a basic knowledge of the art of pharmacy in order to write intelligent prescriptions. He must know the form in which a drug is best administered, what solvents are suitable for a particular medicinal agent, whether two drugs can be placed in solution together without producing an incompatibility, etc. Too often the physician shirks his responsibility in this regard, and resorts to the practice of prescribing "ready-made" mixtures of drugs sold by pharmaceutical houses under trade names. Often the proportion of drugs in such a prepared mixture is not exactly that which is desired. Trade-marked products are also likely to be expensive. The physician gives up his prerogative of individual treatment and does not favor the best interests of his patient when he fails to translate his knowledge of pharmacology into a prescription best suited for the needs of a particular individual. It requires little additional effort in the study of pharmacology to master the few details essential to the correct writing of prescriptions.

Pharmacodynamics is the study of the actions of drugs on the living organism. It is one of the youngest of the experimental medical sciences and dates back only to the latter half of the 19th century. Pharmacodynamics is a border science. It borrows freely both from the subject matter and technics of physiology, physiological chemistry, pathology and bacteriology. It is unique only in that attention is focused on the actions of drugs. As the name implies, the subject is a dynamic one. The student who studies it in a static manner, who merely memorizes the actions of drugs, is foregoing one of the best opportunities for correlating the entire field of preclinical medicine. For example, the mechanism of action of diuretic drugs and their therapeutic indications and limitations can only be fully understood when one has a basic understanding of the physiology of the kidney and the pathological physiology of edema formation. Yet no greater insight can be gained into the physiology of the kidney than that obtainable from a study of the actions of diuretics. As an even more striking example may be cited the action of digitalis on the heart. The study of the cardiac effects of digitalis leads to a better understanding of the physiology of conduction in cardiac muscle, the factors controlling heart rate, diastolic size and cardiac output and the alterations in the functions of the heart and vascular system secondary to congestive heart failure. The pathological physiology of cardiac decompensation can be more thoroughly appreciated by observing the restoration of cardiac function by digitalis and the rapid reversal of events which proceeded slowly over a period of months or years. Again, no better understanding of the physiology of the autonomic nervous system can be obtained than by studying the actions of drugs which prevent the responses of effector organs to nerve impulses, and drugs which mimic the effects of nerve impulses. Conversely, the laborious task of learning the numerous actions of a score or more of autonomic drugs is rendered unnecessary by correlating a basic knowledge of the manner in which these drugs alter the functional activity of structures innervated by autonomic nerves with the known responses of the same structures to nerve stimulation.

Pharmacodynamics also deals with the absorption of drugs, their fate in the body and the mechanism of their excretion. Here a number of principles of physiological chemistry can readily be applied to an understanding of the metabolism of substances foreign to the body.

There are many phases of pharmacodynamics which are of minor interest to the physician, among which is *comparative pharmacology*. From an academic point of view, the action of a drug on frogs may be just as important as its effect on man. The physician, however, is interested in the actions of drugs which are useful in therapeutics, and to him comparative pharmacology is important only in so far as the results obtained have clinical application. Striking advances have occurred in the field of human pharmacology, largely as a result of new methods of experimental approach. When digitalis was first studied, the frog heart was utilized. Much basic information was gained, but the modern interpretation of the actions of the drug on the human cardiovascular system was forthcoming only after the effects of digitalis had been studied in man by means of special technics for measuring cardiac size and output, circulatory velocity, venous pressure, peripheral resistance and changes of conduction in cardiac muscle. As a result, many of the earlier conceptions were discarded or revised. Numerous other instances could be cited in which it was necessary to change the older concepts of the actions of drugs obtained from animal experimentation when the drugs were restudied in man. Therefore, in the following pages, emphasis is placed on human pharmacology.

The subject of comparative pharmacology, however, is not to be neglected. Some of the most esoteric observations on the actions of drugs in lower species can be applied to human pharmacology. For example, the fact that a chicken is anesthetized by barbital for an indefinite period because of its inability to excrete the drug has its clinical counterpart in the patient with inadequate renal function who receives a barbiturate which depends upon renal elimination for its duration of action. The responses of the gastro-intestinal tract of a primitive fish, the tench, to certain autonomic drugs permit broad interpretations which help to clarify the basic mechanism of action of these drugs on smooth and striate muscle.

Another ramification of pharmacodynamics is the correlation of the action of drugs with chemical constitution. This is a basic field which has only begun to be developed, and the one from which the greatest contributions of pharmacology to medicine will probably arise. The relation between chemical structure and pharmacological actions is discussed in connection with the individual drugs. This is done with the realization that many students and physicians have neither the interest nor the chemical background fully to appreciate the importance of the subject. It is hoped, however, that an occasional reader will be stimulated, by the inclusion of this subject, to a deeper interest in pharmacology.

Pharmacotherapeutics is the study of the uses of drugs in the treatment of disease. Pharmacotherapeutics is no longer practiced in an empirical manner, but rather rational drug therapy is based wherever possible upon a correlation of the pharmacodynamic actions of drugs with the pathological physiology of disease. Only in exceptional cases are drugs still used on an empirical basis. In the medical curriculum, pharmacodynamics is usually taught before the student has had clinical courses. For this reason pharmacotherapeutics is often neglected in the teaching of pharmacology on the false premise that the student does not have the necessary clinical background. This is true only if one has empirical therapy in mind. It is during the study of pharmacodynamics that the student has the best opportunity to correlate the actions of drugs with the knowledge that he has already gained of the pathological physiology of disease.

Toxicology is the study of poisons. This broad aspect of pharmacology is discussed separately.

MECHANISMS OF DRUG ACTION

One of the most fascinating and difficult fields of pharmacological research is that which deals with the mechanisms of drug action. In a few instances, the fundamental manner in which a drug produces a given effect is obvious. For example, the efficacy of mercuric chloride as an antiseptic lies in the ability of the mercuric ion to precipitate the bacterial protein. No ready explanation is available, however, to elucidate the manner in which central nervous system depressants produce unconsciousness, or digitalis stimulates the muscle fibers of the heart. In the last analysis, too little is known of cellular physiology to permit an interpretation of the mechanism of action of those drugs which alter cellular functions. However, a few positive statements pertaining to the more general concepts of this subject can be made.

Cellular Response to Drugs. The typical response of a cell to a drug is definitely limited by the functions of that cell. It can be stated with certainty that drugs cannot impart new functions to cells or tissues, but rather can only stimulate or depress cellular activity. The degree to which drugs stimulate or depress can be controlled by dosage and in this way the intensity of action of a drug can be adjusted so as to be of therapeutic value. As pertinent examples may be cited the depressants of the central nervous system which are of clinical value because their degree of activity can be regulated. Any desired intensity of depression can be obtained and this may be varied from sedation through somnolence to anesthesia sufficiently deep to allow performance of major surgical procedures. Conversely, the level of function of the nervous system can be raised by drugs which stimulate the cerebrospinal axis. By a proper selection of drug and dose one may obtain any desired degree of excitation from barely detectable stimulation to severe convulsions.

Disease is often characterized by a change in the functional capacity of certain tissues. For example, congestive heart failure is characterized by an underlying impairment of the contractile power of the myocardium. Inasmuch as a cardiac stimulant can do no more than enable the heart fibers to contract up to the maximal physiological limit of which they are capable, the therapeutic value of digitalis in cardiac decompensation is dependent upon and limited by the inherent functional reserve of the myocardium.

Selective Action of Drugs. Most drugs are selective in action, that is, they affect only a specific tissue. Thus there are drugs which act primarily upon smooth muscle, skeletal muscle, nerve, glands, renal tubules, etc. The antidiuretic principle of the posterior pituitary may be taken as an example of a drug with a highly selective action. As little as 0.0025 mgm of posterior pituitary is capable of inhibiting water diuresis in man. The same dose of the drug affects no other functions of the body. The exact mechanism of this selectivity of action is unknown, but it is believed that there may be a special affinity of a chemical nature between the drug and the responding cells. For example, heart muscle responds to very low concentrations of acetylcholine. It has been calculated that an amount of acetylcholine which could cover only $\frac{1}{6000}$ of the surface of a cardiac fiber can alter the function of that cell. It is therefore believed that acetylcholine acts on special receptors, and inasmuch as the drug is a strong base it is postulated that the receptors may be carboxyl groups. Analogous chemical affinities may exist in all instances in which drugs show selective actions on particular tissues.

Sites of Drug Action. Certain drugs act directly on effector cells; others exert their actions in a remote and roundabout manner. In many instances the exact site of action is unknown. Those substances which act directly upon the responding tissue have two possible sites of action, the surface or the interior of the cell. The very rapid response of effector organs to certain drugs suggests that the site of drug action is extracellular. On the other hand, there is evidence that tissues respond to many chemicals only after they have penetrated the cellular membrane.

Again, the site of action of a drug may be removed from the tissue which ultimately responds to give the desired effect. For example, a substance may lower blood pressure by acting on the vasomotor center. A respiratory stimulant may act on the carotid body rather than on the medulla. Also drugs may exert their effects in an indirect manner by promoting or preventing the action of another substance. Physostigmine stimulates structures innervated by cholinergic nerves not directly but by inhibiting the enzyme which normally destroys acetylcholine. Atropine inhibits the same structures by preventing the access of acetylcholine to the effector cells.

Relation of Chemical Structure to Drug Action. The characteristic action of a drug is intimately related to its chemical structure. The study of the relationship between chemical structure and pharmacological action has led to the synthesis of many valuable therapeutic agents. Sometimes this relationship is a very broad one. For example, in the discussion of the chemistry of the local anesthetics, it is pointed out that, although certain basic structural features are seemingly associated with anesthetic activity, many variations of this basic structure can be made without a loss of characteristic pharmacological properties. The activity of other drugs is lost if the slightest change is made in the configuration of the molecule. In some instances specificity of structure is of such fundamental importance that optical isomers differ in their pharmacological actions. The ergot alkaloids well illustrate this fact. There are many compounds which have multiple actions, and changes in the molecular configuration may alter some of these but not others. Apparently different portions of the molecule are concerned with specific responses. The various derivatives of morphine are excellent examples.

Although it is tempting to attribute the action of a drug to a specific chemical configuration, there are many instances in which drugs of totally different chemical structure possess similar actions. This is especially true of the central nervous system depressants. A comparison of the structures of paraldehyde and barbital would hardly lead one to believe that their pharmacological properties are in many ways similar.

ABSORPTION, DISTRIBUTION, FATE AND EXCRETION OF DRUGS

Absorption. It is of practical importance to know the manner in which individual drugs are absorbed. In many instances the question of absorption influences the route by which a drug is administered. The rate at which a therapeutic agent gains access to the circulation largely determines the latent period between administration and onset of action. The speed of absorption is also a factor in determining dosage. Following are the more important factors which influence the absorption of drugs.

I. *Route of Administration.* Of all factors which influence the absorption of drugs, the route of administration is the most important. Often there is a choice in the route by which a therapeutic agent may be given, and a knowledge of the advantages and disadvantages of the different methods of administration is then of primary importance. The relative merits of the common routes of drug administration may be briefly discussed.

1. *Oral.* The oral route is the most ancient method of drug administration. It is also the safest, most convenient and economical. Drugs given by mouth are for the most part absorbed by the intestinal mucosa, and usually absorption is almost complete by the time the colon is reached. Seldom does an appreciable

portion reach the circulation through the stomach. There are, however, several disadvantages to the oral ingestion of drugs. Irritating substances cannot be given by mouth for they may cause emesis. Also it is not feasible to give treatment by this route to a patient who is vomiting or moribund. Many drugs are destroyed by the action of the digestive ferments before they can be absorbed. Lastly, intestinal absorption may at times be somewhat irregular due to the influence of other substances in the gastro-intestinal tract, variations in the emptying time of the stomach, the pH of the intestinal contents, etc.

2. *Injection.* Many drugs are given by injection. The injection of medicinals has certain advantages over oral administration which at times are of distinct value. In some instances this route of administration is essential in order that the drug be absorbed in active form. Absorption is usually more rapid and more predictable than when a drug is given by mouth. The effective dose can therefore be more accurately selected. In emergency therapy, parenteral administration is particularly serviceable. If a patient is unconscious, uncooperative or unable to retain anything given by mouth, parenteral therapy may become a necessity. On the other hand, there are several disadvantages to the injection of drugs. It is difficult for a patient to perform the injection himself in the event that self-medication is a necessary procedure. Strict asepsis must be maintained in order to avoid infection. An intravascular injection may occur when it is not intended. Parenteral therapy is also more expensive and less safe than oral medication, and lastly, pain may accompany the injection.

Injections may be made into any of the following sites:

(*a*) *Subcutaneous.* Subcutaneous injection is often utilized for the administration of medicinals. It can be used only for drugs which are not irritating to tissue, otherwise a slough may occur. The rate of absorption following subcutaneous injection of a drug is often sufficiently even and slow to afford a fairly sustained effect. Moreover, the rate of absorption from the subcutaneous tissue may be willfully varied by well known technics. The subcutaneous injection of a suspension of a drug in a vehicle in which it is insoluble results in a very slow rate of absorption. As an example may be cited the rate of absorption and duration of action of a suspension of insoluble protamine insulin as compared with that of soluble insulin (Figure 113). The incorporation of a vasoconstrictor agent in a solution of a drug to be injected subcutaneously also retards absorption. This technic is utilized in the combination of epinephrine with local anesthetics (page 289). Lastly, drugs in a solid pellet form may be implanted under the skin and be slowly absorbed over a period of weeks or months. Several hormones may be effectively administered in this manner (Figure 119).

(*b*) *Intramuscular.* Drugs are often injected deep into muscle tissue. From this site drugs in aqueous solution are rapidly absorbed. It is possible to dissolve or suspend drugs in oil and inject them intramuscularly. This leads to a very slow and even rate of absorption. Also irritating substances may be given which cannot be injected subcutaneously.

(*c*) *Intraperitoneal.* Drugs are occasionally injected into the peritoneal cavity. The intraperitoneal injection is seldom employed clinically but it is a common laboratory procedure. The peritoneal cavity offers a large absorbing surface from which drugs enter the circulation rapidly. However, the dangers of infection and adhesions are too great to warrant the routine use of the intraperitoneal route of injection in human beings.

(*d*) *Intravenous.* Drugs in solution can be introduced directly into the circulation, usually into a vein. In this instance the factors concerned in absorption are eliminated and the desired blood concentration of a drug is obtained with an accuracy and immediacy not possible by any other procedure. In most cases the action of the drug is manifest without delay and this is sometimes of importance in emergencies. Also certain irritating and hypertonic solutions can be given only in this manner, for the blood vessel walls are relatively insensitive and the drug, if injected slowly, is greatly diluted by the blood. For example, most of the arsphenamines can be given by no other route. In some instances, as in the production of surgical anesthesia by a barbiturate, the dose of a drug is not predetermined but rather is adjusted to the response of the patient receiving it, and intravenous therapy may then be mandatory in order that the response can be quickly evaluated. On the other hand, there are many dangers which attend intravenous injections. Unfavorable reactions are more prone to occur than when any other route is used. Once the drug is injected there is no retreat, whereas when subcutaneous administration is employed, absorption can be stopped by occluding the venous return from the area of injection. Repeated intravenous injections are dependent upon the patency of veins. Unless specifically indicated, drugs should never be given directly into the blood stream.

(*e*) *Intrathecal.* Certain drugs are injected directly into the subarachnoid space. In such instances, the local actions on the meninges or cerebrospinal axis are desired.

3. *Inhalation.* Gaseous and volatile drugs may be inhaled and absorbed through the pulmonary endothelium or mucous membranes of the respiratory tract and in this way gain rapid access to the circulation. The principles governing absorption and excretion of gases and vapors are discussed under the volatile anesthetics (page 67).

4. *Mucous Membranes.* Absorption of drugs takes place readily through many of the mucous membranes of the body other than that of the alimentary canal, and the more accessible ones are often employed for this purpose. Certain drugs can reach the circulation through the mucous membranes of the rectum, vagina, urethra, conjunctiva, nose and oropharynx. In many instances drugs are applied at these sites for their local action, but on occasion it is the systemic effect which is desired.

5. *Skin.* Few drugs can readily penetrate the intact skin. There are two available procedures, however, by which cutaneous absorption may be greatly increased. Drugs in suitable fatty vehicles can be rubbed into the epidermis and in this manner penetrate into the subcutaneous tissue through the cutaneous glands. This method of administration is known as *inunction.* Drugs which ionize can be made to migrate through the epidermis by means of a galvanic current, a procedure known as *iontophoresis.*

II. *Solubility.* Absorption is dependent upon drug solubility. This does not mean, however, that at the time of administration a drug must be in solution in order that it reach the circulation. Local conditions at the site of absorption alter solubility. Protamine zinc insulin is injected as an insoluble suspension; but in the subcutaneous tissue, solution is slowly effected and absorption proceeds over a long period of time. If calcium salts are given orally, there is little choice between the insoluble carbonate or the soluble chloride for the reactions taking place in the gastro-intestinal tract determine the final composition of the calcium salt. On the other hand, there are certain compounds which are so insoluble and chemically unreactive that they cannot be absorbed. Although the barium ion is highly toxic, large amounts of the insoluble barium sulfate can be given orally with the assurance that no absorption will take place.

III. *Physical State.* The physical state of a drug affects the rate of its absorption. Colloids are more slowly absorbed than crystalloids. Fat-soluble substances reach the circulation more slowly than water-soluble drugs. A drug is more readily absorbed when given in solution than when administered as a dry powder.

IV. *Concentration.* The concentration of a drug influences its rate of absorption. The injection or ingestion of drugs in concentrated solutions usually leads to more rapid absorption than the administration of the same amount in a more dilute form.

V. *Absorbing Surface.* Obviously the extent of the area over which a drug is spread greatly influences the rate of absorption. The large surface of the peritoneal cavity is one of the reasons why intraperitoneal injection results in such rapid absorption. The same is true of the pulmonary endothelium. Drugs are rapidly absorbed from intramuscular sites due to spread of the injected solution along fascial planes.

VI. *Circulation.* The vascularity of the site from which a drug is being absorbed is a major factor influencing the rate of absorption. The circulatory factor can be controlled, often to advantage. For example, it is desirable to keep local anesthetics at the site of injection for the local rather than the systemic action of these compounds is sought. Therefore, as mentioned above, epinephrine is incorporated in solutions of local anesthetics in order to produce vasoconstriction and thus reduce the rate of transfer into the circulation. Conversely, hyperemia enhances the absorption of drugs. Absorption from subcutaneous tissue can be speeded by massage sufficiently vigorous to cause hyperemia. An inadequate systemic circulation greatly retards absorption and intravenous therapy may then be required.

Distribution and Fate. Drugs, as a rule, are generally distributed throughout the body in the medium of the body fluids. Certain agents, however, show definite affinities for particular tissues and accumulate there in high concentrations. This does not necessarily mean that the particular tissue responding to a drug will contain a higher concentration of that drug than do other portions of the body. Often drugs may be selectively distributed in a particular fluid compartment of the body. The bromide ion, for example, remains extracellular in distribution. Many drugs, on the other hand, penetrate cells. Urea and sulfanilamide are outstanding examples of drugs which are distributed throughout all the body fluids.

Often active agents are stored in particular tissues and then slowly released to other organs. For example, large amounts of vitamin A may be retained in the liver. Lead is precipitated in bone, and the element may be stored in the skeletal structure for months after exposure.

Drugs are detoxified or inactivated in the body by a variety of mechanisms. Many are *oxidized.* The action of epinephrine, for example, is of short duration because the compound is readily converted to an inactive oxidation product. Such drugs as acetylcholine and local anesthetics are inactivated by *hydrolysis.* Other substances may be *reduced. Conjugation* is the mechanism for the detoxification of many drugs. For example, phenol is conjugated with glycuronic and sulfuric acids before excretion. There are many drugs which resist destruction in the body and are active until they are eliminated through the various channels of excretion.

Often a particular organ is responsible for the detoxification of a drug. Knowledge of this is of practical importance for, if the function of that organ is impaired, detoxification does not proceed in a normal manner and the degree or duration of activity of the drug involved may be different from that desired. To cite a specific example, certain ultrashort-acting barbiturates used intravenously as general anesthetics for minor operations are destroyed by the liver. If hepatic function is seriously impaired, the duration of anesthesia may be abnormally prolonged.

Excretion. Each drug is excreted in a characteristic manner. It is often of considerable importance to know the route and rate of excretion of a drug. Certain therapeutic agents may be removed from the body only by a single obligatory channel. Others may be eliminated by a number of routes. As has already been stated, a drug may be excreted unchanged, or in the form of some type of conjugation or breakdown product. The most important organs for the excretion of drugs are the kidneys, colon and lungs. All drugs which can traverse the capillary membrane appear in the urine, for few substances are completely reabsorbed by the renal tubules. However, in some instances the renal route of excretion is relatively unimportant. Many of the heavy metals are eliminated in part through the large bowel. Other agents may be excreted in the bile and in this way gain access to the feces. There are a few instances in which drugs excreted by the bile are reabsorbed by the intestines in an active form and thus their duration of action is greatly prolonged. The gases are almost entirely excreted by the lungs. Drugs can appear in any of the secretions of the body. Many substances are detectable in the saliva, and heavy metals may be present in this fluid in sufficient concentration to cause a metallic taste and induce ptyalism and gingivitis. During lactation certain drugs gain access to the milk. Sweat may also contain appreciable amounts of many drugs and if these substances are irritating, skin eruptions may occur from excretion by this route. Drugs have also been detected in the lacrimal secretion. Lastly, most drugs cross the placental barrier and gain access to the fetal circulation. For example, the use of central nervous system depressants, especially morphine, during labor may delay the onset of spontaneous respiration in the new-born infant.

Drugs are concentrated at the site of excretion and therefore many of the symptoms of poisoning are referable to the organs of elimination. In cases of poisoning by mercury, severe renal damage and colitis occur due to the excretion of the metal by the kidneys and colon. It is of prime importance, therefore, to protect the organs of excretion.

A careful therapeutist never administers a potentially toxic drug unless the organ essential for its excretion is functioning properly. For example, certain organic mercury compounds are potent diuretics. They are not to be given, however, unless renal function is adequate.

FACTORS MODIFYING DRUG ACTION

Many factors modify the actions of drugs and must be taken into account in the therapeutic use of medicinal agents.

I. Dose. Obviously the dose of a drug greatly influences its actions. The amount of a drug which causes untoward symptoms in the average individual is known as the *toxic dose;* the amount which kills, the *fatal dose*. The *minimal lethal dose* (M.L.D.), as ascertained experimentally on animals under controlled conditions, represents the amount of a drug which is fatal to 50 per cent of the animals. The *minimal dose* of a substance is the smallest amount which has therapeutic effects; the *maximal dose*, the largest amount that can be tolerated without toxic symptoms. Somewhere between the minimal and maximal doses of a drug lies the optimal or *therapeutic dose*. The figure obtained by dividing the M.L.D.

by the therapeutic dose is known as the *therapeutic ratio.* Obviously the higher this ratio, the safer is the drug to use.

Certain drugs have a biphasic action, that is, at two different dose levels they exert different therapeutic effects. Atropine is a striking example. Small amounts stimulate the vagus centrally and slow the heart rate, whereas a larger dose frees the heart from vagal inhibition and thus speeds the cardiac rate.

The therapeutic dose of a drug is influenced by many factors which are always considered before a drug is prescribed.

(*a*) *Age.* As a rule, children are more sensitive to drugs than are adults, and there are certain agents to which very young individuals are abnormally susceptible. For example, infants are markedly sensitive to central nervous system depressants, especially morphine. Several formulas are available for calculating doses for children. The three best known are the following:

Clark's rule: $\dfrac{\text{weight of child}}{150} \times \text{adult dose}$

Young's rule: $\dfrac{\text{age of child}}{\text{age} + 12} \times \text{adult dose}$

Cowling's rule: $\dfrac{\text{age of child at next birthday}}{24} \times \text{adult dose}$

Clark's rule is based on weight in pounds alone, the other two on age alone. Other rules combine both factors. All apply fairly well to children younger than 10 years of age. Clark's rule is probably the most serviceable. Doses for *infants* should be learned as such and not calculated by formula.

(*b*) *Body Weight.* The ratio between body weight and the amount of drug given determines the concentration which can be attained in the body. Therefore the average dose of a drug should be suitably changed when one is prescribing for an abnormally light or heavy individual.

(*c*) *Sex.* Women are more susceptible to the action of certain compounds than are men and in some instances this difference in responsiveness is sufficient to demand reduction in dosage. During pregnancy, for example, caution is necessary in the administration of drugs affecting the uterus.

(*d*) *Time of Administration.* The time at which a drug is administered sometimes influences dosage. This is especially true for oral therapy in relation to meals. Absorption proceeds more rapidly if the stomach and upper portion of the intestinal tract are free of food and an amount of drug which is active before may be ineffective if given after a meal. On the other hand, in the case of irritating drugs, much larger amounts can be tolerated if food is in the stomach.

(*e*) *Route of Administration.* Inasmuch as rate and extent of absorption differ with the route of administration, dosage must be adjusted to take this factor into account. The intravenous dose of a drug is often somewhat smaller than the subcutaneous, and this in turn is usually smaller than the oral.

(*f*) *Rate of Excretion.* If chronic medication is necessary, the rate of excretion or destruction of a drug is a necessary consideration in determining dosage. If a drug is repeatedly given and absorbed at a rate more rapid than it can be destroyed or excreted, the concentration in the body will rise and toxic symptoms will occur. This is known as *cumulative action* (Figure 1). Often it is desirable to maintain an even concentration of drug in the body in order to obtain a constant level of therapeutic effect. Once this level is attained, the so-called "*maintenance dose*" can be determined, that is, the daily dose of drug which balances the rate of elimination and destruction.

(*g*) *Drug Combinations.* When drugs having the same type of action are given in combination, the average dose of each should be reduced. Certain terms are used to describe the various ways in which drugs may act together. When the combined action of two drugs administered at the same time is equal to the algebraic sum of their individual effects the response is known as *summation*. Summation can be negative or positive. Negative summation is also termed *antagonism*. The stimulants and depressants of the central nervous system are outstanding examples of antagonistic groups of drugs. Positive summation is known as *synergism*. Most drugs producing the same type of response are synergistic when prescribed together. It is sometimes advantageous to prescribe two synergistic drugs rather than a single agent. By this procedure, inasmuch as only one-half of the therapeutic dose of each is employed, it may be possible to obtain a greater margin of safety if the toxic effects of the individual components are exerted on different physiological systems. Another advantage of drug combinations is that

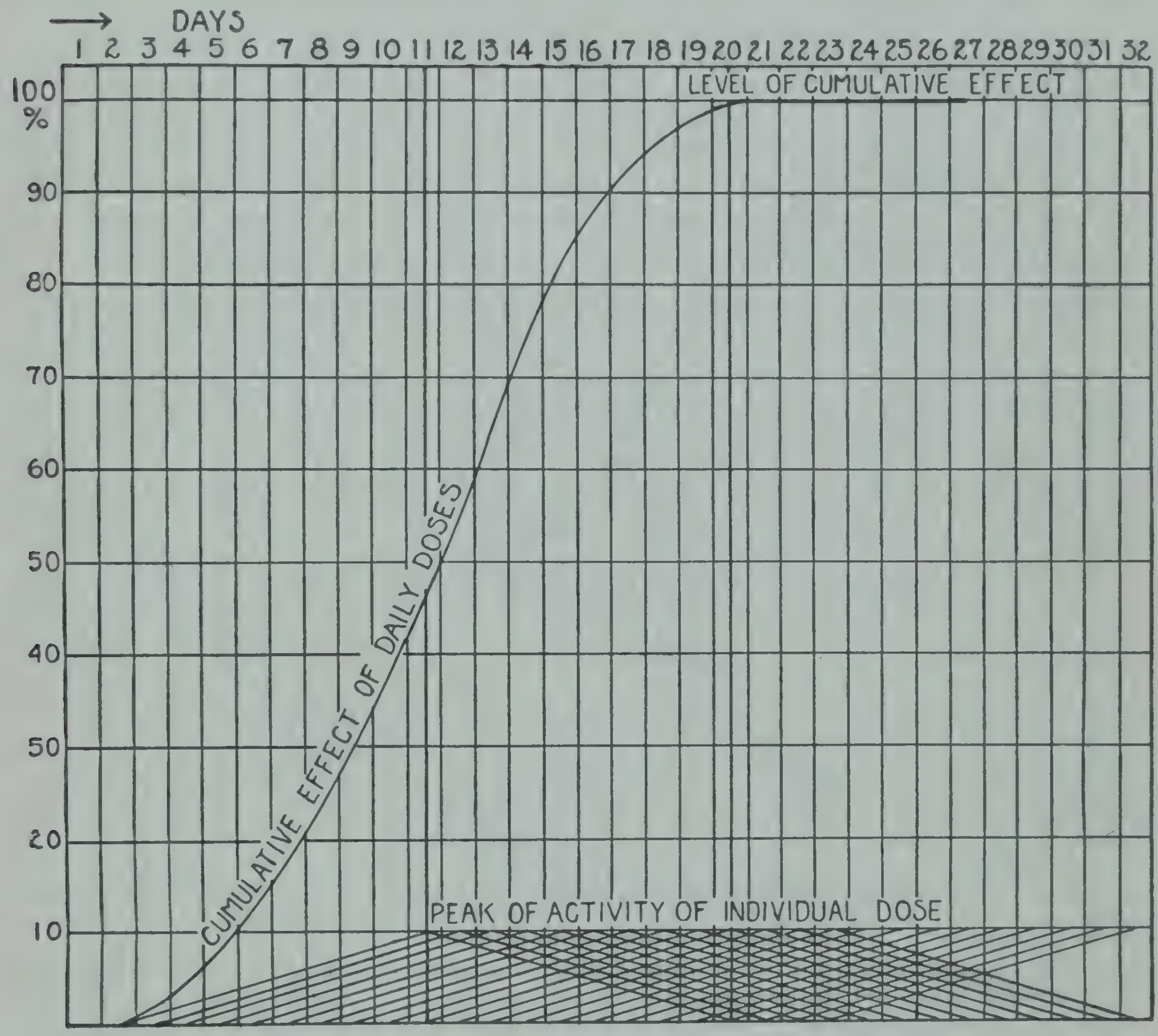

Figure 1. *Cumulative drug action.*

Schematic illustration of the effects of daily doses of desiccated thyroid, a drug which characteristically exhibits cumulative action. The effect of a single dose is not manifest until after 24 hours and does not reach its peak until 10 days later. For the sake of simplification it is assumed that the action of the drug disappears within 10 days and that the individual daily doses are merely additive. Therefore the plateau level of cumulative effect will not be reached until about the 20th day, and the ultimate effect of a given dose level cannot be determined in less time. (After *Therapeutic Notes*. Courtesy of Parke, Davis & Co.)

drugs which produce the same end-result may have entirely different mechanisms of action and in this way combine very effectively. Also two drugs having the same therapeutic effect may differ with respect to the rapidity of onset and duration of action. For example, if one drug has a rapid onset but short duration of action and another has a slow onset and prolonged duration of action, their synergistic action will be characterized by a rapid onset and long duration (Figure 2).

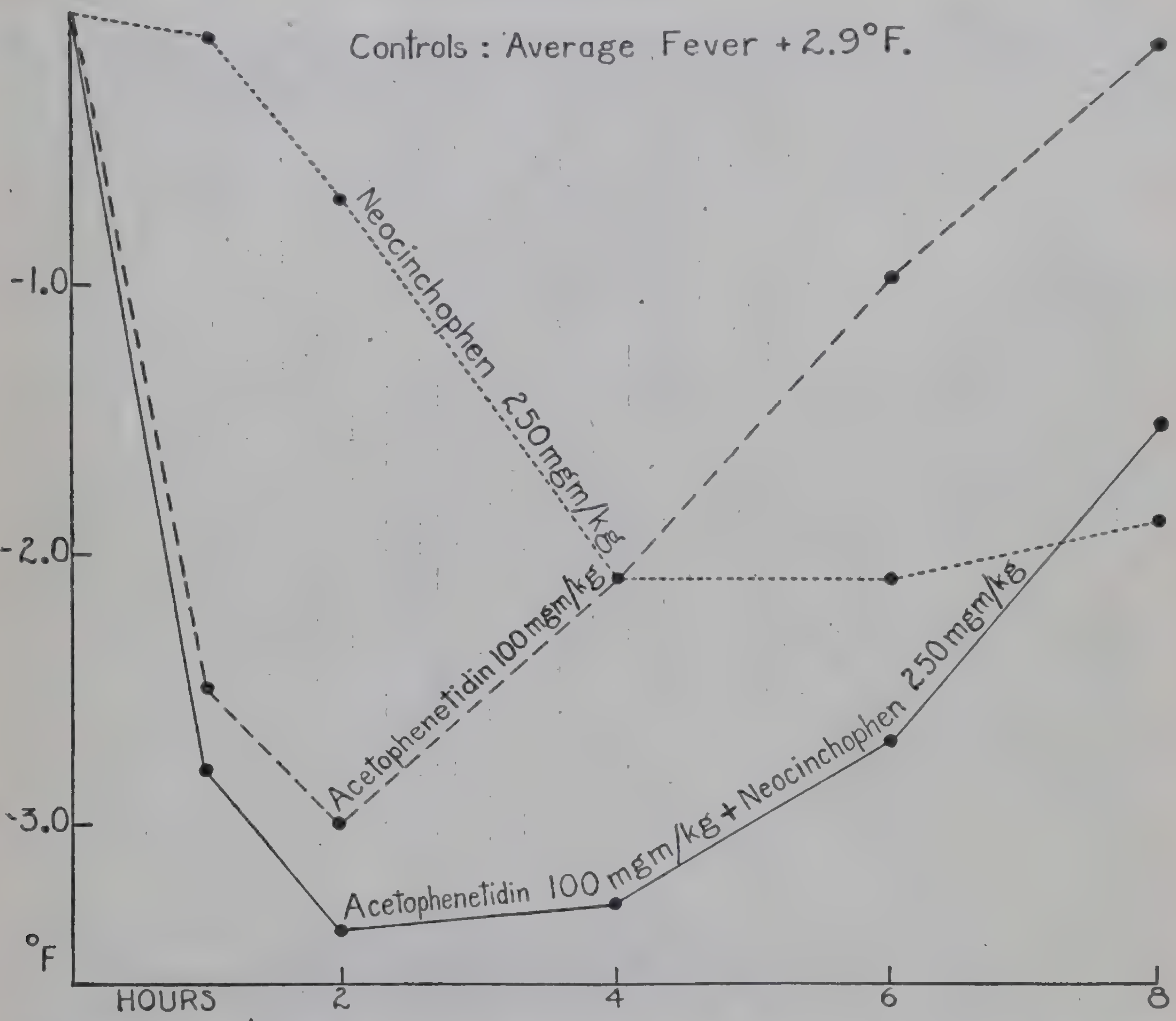

FIGURE 2. *Antipyretic experiment illustrating the phenomenon of positive summation (synergism).*

Observations were made on rats fevered by the subcutaneous injection of yeast suspension 14 hours prior to the administration of the antipyretic drugs. The latter were administered in an aqueous suspension by stomach tube. The antipyretic effect is measured by calculating the difference between the rectal temperatures of fevered control and treated experimental animals. Acetophenetidin is a powerful antipyretic with rapid onset and short duration of action. Neocinchophen is slowly absorbed and its action is less rapid in onset and longer in duration. When acetophenetidin and neocinchophen are given together, positive summation is evident in the rapid onset and prolonged duration of action, the antipyretic effect at any point being approximately the sum of the effects of the individual drugs.

There are instances in which the combined action of two drugs is greater than that which can be anticipated from the sum of their individual actions. This is known as *potentiation*. For example, the administration of acid-forming saline diuretics prior to a mercurial diuretic results in a greater volume of urine than is predictable on the basis of individual effects (Figure 69).

II. Tolerance. Tolerance may be acquired for many drugs and if this occurs, the dose must be progressively increased in order to maintain a given therapeutic response. The nitrites represent a group of drugs to which tolerance develops. When prescribing nitrites for hypertension one starts with the lowest effective dose because this may shortly have to be increased as tolerance develops.

Occasionally a person is tolerant to a drug which he has never taken before. This is known as *individual tolerance*. Certain species are relatively insensitive to particular drugs. This is known as *species tolerance*. For example, rabbits show a marked species tolerance to belladonna alkaloids. Resistance to the action of certain drugs sometimes results in tolerance to chemically related compounds having a similar action. This is known as *cross tolerance*. The patient who as a result of continued use is tolerant to alcohol may also be tolerant to tribromethylalcohol (avertin), ether and related central nervous system depressants.

The continued use of some drugs may lead to *habituation*, a condition which is characterized by a psychic craving manifested when the drug is withdrawn. A large number of drugs are capable of producing habituation, and if sufficient psychic influence is brought to bear, habituation may occur to pink water. The repeated administration of certain drugs, notably morphine and related alkaloids, cocaine and alcohol, may result in *addiction*. In this instance, withdrawal results not only in psychic craving but also in a characteristic abstinence syndrome of organic origin which is manifested in distorted physiological processes. Evidently in the addicted individual the presence in the body of the addicting drug is necessary to maintain normal cellular functions. The only reliable test for addiction is withdrawal of the drug and close observation of the individual for the appearance of characteristic abstinence symptoms and signs. Tolerance to a drug need not necessarily be associated either with habituation or addiction.

III. Idiosyncrasy. *Idiosyncrasy* is an abnormal or unusual response to a drug, and may occur even to very small doses. It is one of the factors modifying drug action which usually cannot be anticipated in advance. An abnormal response may occur after a drug has been administered for the first time or it may suddenly appear during an uneventful course of chronic medication. The unusual responses associated with the use of drugs have been learned only from experience. In many cases, idiosyncrasy may manifest itself in such a subtle manner that any association of the drug with the untoward reaction may escape recognition until the drug has been in general use for many years. Such was the case with cinchophen which was employed in the treatment of gout for 17 years until it was finally appreciated that in some individuals it may cause a fatal toxic hepatitis.

Idiosyncrasy may manifest itself in many ways. A rare individual is excited rather than depressed by morphine. A therapeutic dose of aspirin in a susceptible person may cause a severe anaphylactic response. Aminopyrine may inhibit the maturation of polymorphonuclear leukocytes to such a degree that severe agranulocytosis results. Arsphenamine in isolated instances may depress all cellular elements of the bone marrow and cause an aplastic anemia.

IV. Influence of Pathological States. The actions of certain drugs are considerably modified by pathological conditions. Antipyretic agents cause a marked fall in body temperature in an individual with fever. but if the same dose is given to a person whose temperature is normal no noticeable decrease is obtained. A therapeutic dose of a diuretic drug produces only a slight augmentation in the urine flow of a normal individual but may promote the excretion of several liters of fluid in an edematous patient. An individual with hyperthyroidism is responsive to a dose of epinephrine that would scarcely affect a person with a normal metabolic rate, but on the other hand he can tolerate larger doses of morphine than can normal individuals. Conversely, the patient with myxedema may be seriously narcotized by a dose of morphine which normally is only moderately depressant. In many cases it is of utmost importance to be familiar with the unusual modifications of drug action which certain pathological conditions can produce.

V. Cumulative Action. The cumulative action of a drug may modify its effects greatly, changing a therapeutic action into a toxic one. If a drug is excreted slowly, its continuous administration may build up a sufficiently high concentration of drug in the body to produce poisoning.

CHEMICAL CLASSIFICATION OF DRUGS

From a chemical point of view, drugs may be classified in many ways. A major distinction may be made between synthetic drugs and those which occur naturally. In the past, the major advances in pharmacology were made as the properties of drugs of natural origin were studied and applied in therapy. This field has been largely exhausted, with the exception, however, of the hormones and vitamins, natural products of animal and plant origin. The study of synthetic drugs is a very young field of investigation. The recent additions to the growing list of synthetic preparations, such as cyclopropane, sulfanilamide, sulfapyridine, dilantin, stilbestrol, desoxycorticosterone, mapharsen, carbarsone, choline esters, prostigmine, synthetic morphine derivatives, etc., predict an exciting future and broadening scope for pharmacotherapeutics.

Synthetic Drugs. It is of little importance to classify synthetic drugs from a chemical point of view. They range from simple inorganic preparations to complex aliphatic and aromatic organic compounds.

Natural Drugs. Natural drugs of plant origin lend themselves more readily to chemical classification. The majority of medicinal substances obtained from plants fall into the following groups: *alkaloids, neutral principles, acids, tannins, fats, waxes, fixed oils, volatile oils, resins, oleoresins* and *balsams*. Only the first two groups require further definition and discussion.

Alkaloids. The majority of the important drugs obtained from plants are in this category. The alkaloids are basic organic compounds containing nitrogen. The alkaloids are so named because alkaloidal solutions are weakly alkaline in reaction. Alkaloids form salts with acids by addition on the nitrogen group. They have characteristic solubilities, the alkaloidal salts being soluble in water, and the free bases in organic solvents. A few alkaloids are liquid in their basic form but the great majority are solids. All are bitter to the taste. They have distinguishing names in that all end in *"ine."* Morphine and atropine may be named as outstanding examples of plant alkaloids. Many synthetic substances have the chemical characteristics of alkaloids and could be so classified.

Neutral Principles. Neutral principles, in contrast to alkaloids, are neutral in reaction. The names of the drugs in this class end in *"in."* The neutral principles have no distinguishing chemical features aside from their neutral reaction and embrace a wide variety of chemical substances. Included among the neutral principles are the *glycosides.* Glycosides are neutral principles which contain a carbohydrate molecule in conjunction with one or more other chemical bodies.

The carbohydrate molecule is not necessarily essential for the action of a glycoside and may be removed by hydrolysis to leave an active *aglycone*. Outstanding examples are the cardiac glycosides, the chemistry of which is discussed in detail under digitalis (page 501). An example of a neutral principle that is not a glycoside is picrotoxin.

PHARMACEUTICAL PREPARATIONS OF CRUDE DRUGS

It is not always feasible to isolate pure drugs from natural sources and many drugs of plant or animal origin are administered in the crude form. Crude preparations of natural drugs are often referred to as *galenicals*. This term derives its name from Galen who described methods for the preparation of many crude drugs, and it is now employed to distinguish the following classes of medicinals from those obtained by more elaborate chemical procedures:

(1) **Tinctures.** Tinctures are alcoholic or hydro-alcoholic solutions of the active principles of animal or vegetable drugs. The proportion of drug represented in the different kinds of tinctures is not uniform but varies according to the established standards for each. For potent drugs, the usual procedure is to extract by percolation 10 grams of the crude drug for each 100 cc of the final alcoholic solution.

(2) **Extracts.** Extracts are concentrated preparations of vegetable or animal drugs obtained by extracting the active constituents of the respective drugs with suitable solvents, evaporating all or nearly all of the solvent and adjusting the residual masses or powders to the prescribed standards.

(3) **Fluidextracts.** Fluidextracts are liquid preparations of vegetable drugs containing alcohol as a solvent, as a preservative or both, and made so that one cc contains the therapeutic constituents of one gram of the standard drug which it represents.

(4) **Decoctions.** Decoctions are liquid preparations prepared by extracting a crude drug with actively boiling water. One liter of a decoction is usually prepared from 50 grams of crude drug.

(5) **Infusions.** Infusions differ from decoctions in that the crude drug is extracted with water without active boiling. The water may be at any temperature depending upon the stability of the drug to heat.

In many instances crude drugs are employed after no more formal procedure than drying and pulverizing the active portion of a plant or animal tissue.

BIO-ASSAY OF DRUGS

Crude preparations of drugs often must be assayed in order to determine their drug content. In the event that the chemical composition of the active ingredient of a crude drug preparation is known, it may be possible to determine the activity by means of chemical analysis. Sometimes it suffices to determine the activity of a crude drug merely by analyzing for a particular chemical group or element. Thus the potency of *Thyroid*, U.S.P., is assayed on the basis of the iodine content of the dried gland.

Often, however, no chemical method is available to determine the pharmacodynamic activity of crude preparations and one must resort to *bio-assay*. Bio-assay is the measure of the concentration of a specific active ingredient of a crude drug, and is performed by determining the amount required to produce a definite effect on a suitable test animal or organ under standard conditions. The activity of many important therapeutic agents is standardized in this way. The usual technic is to compare the action of the drug being assayed with that of a known standard under rigidly controlled conditions. The method of bio-assay employed differs for individual drugs and is usually based upon the therapeutic action of that drug. For example, the activity of an insulin preparation is determined by its ability to lower the blood sugar in rabbits. The vitamin D activity of cod liver oil is determined by the ability of the oil to cure rickets in rats. A toxic property of the drug, however, may be used for bio-assay. Thus the potency of powdered digitalis is measured by its toxic effect on the frog heart. In one instance, a bio-assay is conducted on human beings. Because no suitable laboratory test animal is available for the assay of antianemia substances, liver and stomach preparations are tested for their potency on patients with classical pernicious anemia in relapse.

The activity of a crude drug which is bio-assayed is usually expressed in terms of *units*. Both the unit and method of assay are rigidly defined, in some instances by international committees so that universal standards exist. Official drugs have legally required methods of assay, which lead to uniformity, at least, within a given country. Unfortunately, in the case of many of the newer preparations, notably the endocrines, there is no prescribed method of assay or commonly accepted unit and the commercially available products vary considerably in strength. As a drug gains wide use, however, this condition is frequently rectified by the appointment of a suitable board or commission to solve the problem of assay and unitage.

The methods of bio-assay of individual drugs are discussed in the text as occasion arises.

OFFICIAL AND NONOFFICIAL DRUGS

Once the physician has decided upon a course of therapy for his patient, it is imperative that the patient receive exactly what has been prescribed. Drugs must therefore be of a uniform quality. The physician may readily assure himself of this by prescribing official drugs.

An *official drug* in the United States is one which is included either in the United States Pharmacopeia (U.S.P.), The National Formulary (N.F.) or The Homeopathic Pharmacopeia. Other nations have similar drug standards; the official one in the British Empire is the British Pharmacopeia (B.P.).

United States Pharmacopeia. The United States Pharmacopeia (usually designated as the U.S.P.) is a publication in which the approved therapeutic agents used in medical practice are described and defined with respect to source, chemistry, physical properties, tests for identity, tests for purity, assay, method of storage and average therapeutic dose. Most of the preparations in the U.S.P. are single drugs. In the case of those which must be compounded, instructions are given for their preparation. The object of the U.S.P. is to provide standards for drugs and medicines of therapeutic usefulness or pharmaceutic necessity. The first Pharmacopeia in the United States was published in 1820, and since that time numerous revisions have appeared. The current edition, U.S.P. XI, became official in 1936. It is the practice to revise the Pharmacopeia at 10 year intervals but, in the interim, *Supplements* are now published which include new preparations. In this manner the Pharmacopeia can be kept abreast of rapid advances in pharmacotherapeutics. Supplements to the U.S.P. XI appeared in 1937 and 1939. As an indication of the speed with which outstanding new drugs are included in the Pharmacopeia, the following agents appearing in the 1939 Supplement may be mentioned: Ascorbic Acid, Nicotinic Acid, Pentobarbital Sodium, Cyclopropane, Sulfanilamide and Thiamine Hydrochloride.

The U.S.P. is revised by a special Pharmacopeial Committee, the members of which donate their services in the interest of the important function which they serve. The Pharmacopeial Committee consists of outstanding pharmacologists, physicians and pharmacists. The general committee on revision is assisted by numerous subcommittees and advisory boards. As examples may be cited the *U.S.P. Vitamin Advisory Board,* the *U.S.P. Anti-Anemia Products Advisory Board,* the *U.S.P. Committee on Cardiac Drugs,* etc.

The drugs included in the U.S.P. are *official* by virtue of the fact that the Federal Pure Food and Drug Act designates the Pharmacopeia as one of the volumes defining the official standards of purity for drugs. Thus the physician, by prescribing official drugs, is assured of their quality and uniformity.

Patented drugs cannot be made official drugs for the reason that the patentee is the sole arbiter for the standards of the product. They cannot be included in the U.S.P. until patents expire; this explains why many outstanding therapeutic agents, as for example insulin, are not official. Neither can a drug be labeled U.S.P. which does not bear the official name of the drug.

The National Formulary. The National Formulary (usually designated as N.F.) was first published in 1888 under the name "National Formulary of Unofficial Preparations." At that time it contained only formulas for preparations of drug mixtures. Standards for those drugs included in the formulas but not listed in the U.S.P. were given. The publication became an official drug standard when so designated by the Federal Pure Food and Drug Act of 1906, after which the name was changed to *The National Formulary.* The current edition is the N.F. VI, published in 1936.

The National Formulary is published by the American Pharmaceutical Association. It is prepared by a committee consisting mainly of outstanding pharmacists. The purpose, as defined in the National Formulary, is ". . . to supply definite formulas for preparations that are sufficiently used in medical practice in the United States, or its possessions, and for which formulas are not included in the Pharmacopeia of the United States, Eleventh Revision; and to provide standards and tests for the identity, quality, and purity of the ingredients used in these formulas, and for such other medicinal materials as are frequently called for in the pharmacies of the United States for which standards are not provided in the U.S. Pharmacopeia XI, so that uniformity in the physical properties and therapeutic action of these preparations will be assured."

The N.F. supplements the U.S.P. in many important ways. The Pharmacopeia is a more valuable and critical publication in that the therapeutic worth and the toxic potentialities of a drug are considered before an agent is included. The N.F. contains drugs on the basis of demand. For example, *Cinchophen,* U.S.P. X, was deleted from the U.S.P. XI because of the propensity of the drug to damage the liver. Cinchophen is still employed, however, and in order that there may be official standards for its purity, the drug is included in N.F. VI. Likewise, many other drugs which have been deleted from the U.S.P. appear in the N.F. The National Formulary also differs from the Pharmacopeia in that it contains principally formulas of drug mixtures rather than monographs on discrete drugs. Thus the majority of the so-called *official prescriptions* are to be found in the N.F. As in the case of the Pharmacopeia, only non-patented drugs under their official titles are admitted to the N.F.

The Epitome of the U.S.P. and N.F. The physician has little need for the detailed information contained in the U.S.P. and N.F. but rather he is chiefly concerned with knowing which drugs are official and a few pertinent facts concerning their physical and chemical properties. The American Medical Association publishes a small, inexpensive and valuable volume known as the *"Epitome of the United States Pharmacopeia and National Formulary."* In it are given the titles of the drugs included in each of the official publications and such facts as are useful to physicians.

Official Nomenclature. Drugs included in the U.S.P. and N.F. bear official titles. Many drugs have one or more official synonyms. Many pharmaceutical concerns, however, prefer to market their official drugs under trade names rather than official names. This fact immediately necessitates wide advertisement of the trade name of the drug to the medical profession so that the drug will be purchased by its trade name rather than by its official title. Naturally, advertising incurs an expense which must be borne by the person who eventually buys the trade-marked product. A drug sold under a trade name is usually considerably more expensive than the identical substance bearing only an official title. Even when a physician unwittingly prescribes an official drug by its trade name, the pharmacist is obligated to fill the prescription with the brand of drug ordered, thus entailing unnecessary expense for the patient. There is little reason for the physician to be unaware of the official nature of drugs marketed under trade names for the official nomenclature must by law be stated on the label.

Nonofficial Drugs. Much of the current research in the development of therapeutic agents is performed in the laboratories of or subsidized by reputable drug firms. In legitimate return for his investment, the manufacturer can patent his product and enjoy the exclusive rights of its manufacture and sale. Many drug houses release a new therapeutic agent only after it has received a thorough experimental study and clinical trial, announce the chemical composition of the agent and are circumspect in regard to the claims that are made for the drug. Not all patented drugs, however, are promoted in this manner. Some are marketed with little experimental evidence of their effectiveness and unwarranted and unsupported claims are made for them.

The physician's concern is not with the possibility of overlooking a significant new therapeutic advance. Rather, his problem is to differentiate between the extravagant and truthful claims in the advertising material with which he is deluged. This can be accomplished by a meticulous time-consuming study of the literature pertaining to the pharmacological actions of and therapeutic results obtained with the drug in question. The validity of the conclusion depends upon the ability of the physician critically to select and to evaluate the cogent evidence for and against the new therapeutic agent. An alternative course is to depend upon the judgment of the *Council on Pharmacy and Chemistry* of the American Medical Association.

New and Nonofficial Remedies. The Council on Pharmacy and Chemistry (subsequently referred to as the *Council*) is composed of a group of outstanding physicians and scientists. The Council publishes the book entitled *New and Nonofficial Remedies* (*N.N.R.*). Included in N.N.R. are descriptions of proprietary articles which have been *accepted as conforming to the rules of the Council,* such simple non-proprietary and nonofficial substances as seem of sufficient importance to warrant their inclusion, and simple pharmaceutical preparations, the inclusion of which is believed to give useful information to physicians. The *rules of the Council* are designed primarily to protect the medical profession and the public against fraud, undesirable secrecy and objectionable advertising in connection with proprietary medicinal articles. The rules can be found in the introduction to N.N.R. The descriptions of drugs include chemical and physical properties, tests for identity and purity, dosage, preparations, actions and uses.

There is no compulsion for manufacturers to submit their drugs to the Council for inclusion in N.N.R. However, the opinions of the Council are so widely accepted by the members of the medical profession that many drug distributors attempt to obtain for their proprietary products the seal of acceptance of the Council on Pharmacy and Chemistry of the American Medical Association. Thus there are few proprietary drugs of outstanding value which have not been submitted to the Council. There are many reasons why a drug may be rejected by the Council. Usually it is because it has little therapeutic worth. Occasionally however, a drug of genuine value is rejected because of the name given to it, the claims made for it, or the manner in which it is advertised. Usually these difficulties are ironed out by consultation between the distributor and the Council, and it is only an occasional proprietary drug of proved worth which is not included in N.N.R.

New and Nonofficial Remedies is published annually, shortly after the beginning of the year, and includes preparations accepted up to the beginning of that year. A supplement dealing with preparations accepted during the following six months is also released. The N.N.R. is sold by the American Medical Association at a nominal price. Throughout the year, notification of acceptance or nonacceptance of individual drugs is published in the *Journal of the American Medical Association*. Thus little time need elapse before an outstanding new drug is accepted by the Council. The *Reports of the Council,* usually released at the time a drug is accepted or rejected, are valuable sources of current pharmacological information. They are written either by Council members or by outstanding consultants who are specialists in the field of medicine to which the drug under consideration pertains.

The protection that the Council affords the physician cannot be overestimated. At the price of only a slight delay, he can employ proprietary drugs with the assurance that they have been approved by specialists best equipped to pass judgment on a particular therapeutic agent. By prescribing Council-accepted drugs, not only does the physician know that he is using an agent which meets the claims of the manufacturers, but also that the drug has been carefully scrutinized in regard to its potential toxic effects. It is only the research pharmacologist in conjunction with the clinical specialist who should be entrusted with the evaluation of new drugs, and for the average physician to relegate this responsibility to others, as he does when he gives preference to Council-accepted preparations, is not a discredit to his pioneering spirit but rather a favorable reflection on his scientific judgment.

THE FEDERAL FOOD, DRUG AND COSMETIC ACT

The current Federal Food, Drug and Cosmetic Act became law in 1938. It replaced the original act passed in 1906. The act is designed for the protection of public health, but it also serves to protect the physician from unethical practices of irresponsible drug manufacturers. Enforcement of the law is entrusted to the

Food and Drug Administration of the Department of Agriculture. The physician should be familiar with the provisions of this act and assist in every way possible in its enforcement. Features of the act of particular interest to the medical profession have been summarized by Klumpp (1939). Following are some of its major provisions pertaining to drugs:

(1) It brings under governmental control drugs used in the diagnosis of disease and drugs intended to affect the structure or any function of the body.

(2) Prohibits traffic in drugs and devices which are dangerous to health under conditions of use prescribed in the labeling.

(3) Prohibits traffic in new drugs unless such drugs have been adequately tested to show that they are safe for use under the conditions of use prescribed in their labeling; authorizes exemption from this requirement of drugs intended solely for investigational use by qualified scientific experts.

(4) Requires drugs intended for use by man to bear labels warning against habit formation if they contain any of a list of narcotic or hypnotic habit-forming substances, or any derivative of any such substance which possesses the same properties.

(5) Requires the labels of nonofficial drugs to list the names of the active ingredients, and in addition to show the quantity or proportion of certain specified ingredients.

(6) Requires the labeling of drugs and devices to bear warnings against use in those pathological conditions or by children when such use may be dangerous to health, or against unsafe dosage or methods or duration of administration or application, in such manner and form as are necessary for the protection of the user.

(7) Requires labels of official drugs to reveal any differences of strength, quality or purity from the official standards.

(8) Requires official drugs to be packaged and labeled as prescribed by the Pharmacopeia and National Formulary.

(9) Declares nonofficial drugs illegal if the standard of strength thereof differs from, or the purity or quality falls below, the standard claimed.

(10) Requires that antiseptics possess germicidal power.

The above provisions do not apply to physicians' prescriptions. The law assists the physician in that it rigidly controls the standards, purity and composition of drugs and drug mixtures. In the last analysis, the law is designed to protect the layman who insists in indulging in self-medication, but it cannot compare in its results with the protection afforded by proper medical care on the part of a physician.

GENERAL PRINCIPLES OF TOXICOLOGY

Toxicology is the science of poisons. The subject matter of this broad branch of pharmacology includes the origin, chemical properties, toxic actions and detection of poisons, and the treatment of intoxications produced by them. A poison is difficult to define. Even such a benign substance as water can be toxic if administered in sufficiently large amounts. Many definitions, therefore, limit the term poison to those substances which cause toxic effects in amounts under 50 grams, but this is quite arbitrary. Also only substances acting chemically on body tissues are usually considered poisons. Ground glass, for example, would be excluded from consideration as a poison by this restriction. Lastly, in order that a drug may be classed as a poison, the toxic action must represent its usual effect. A person may be allergic to a certain protein, yet this protein is toxic only under special circumstances and therefore cannot be considered as a poison. The following definition cited by Peterson, Haines and Webster (1923) takes all these factors into account: "*A poison is a substance, which, when introduced into the body in relatively small quantity and acting chemically, is capable of producing death or serious injury to health in the case of an ordinary individual in average health.*"

It is evident that few drugs employed in therapeutics are excluded even by the most rigid interpretation of the above definition. All drugs are potential poisons and the separation of their pharmacological and toxicological properties is often difficult and sometimes impossible or unprofitable. Therefore at this time only the broad principles of toxicology are discussed. The symptoms and treatment of poisoning by specific agents appear under the discussion of the individual drugs.

The physician is not interested in all aspects of toxicology. The detection of poisons is an intricate procedure which demands specialized training. Rather the practitioner devotes his attention to the symptoms, diagnosis and treatment of poisoning. However, in the event of poisoning, the physician is usually one of the first present and therefore certain obligations and duties fall upon him.

Duties of the Physician in Poisoning Cases. If the circumstances surrounding a case of poisoning are at all suspicious, the physician has a duty to the State as well as to the patient. He should therefore preserve any evidence which may prove of special value. This includes any vomitus, urine or stool that is passed, and any food or medicine that could possibly have contributed to the symptoms. The specimens should be stored in clean glass jars and sealed in such a way as to preclude the possibility of tampering. The samples should then be transferred to the proper authority for subsequent analysis. At the first available opportunity, the physician should make accurate written notes of the important aspects of the case. This may be of great value if the case should become medico-legal and testimony in court is necessary. Also the physician's accurate observations of the patient are of great assistance to the toxicologist, whose task is simplified if the symptoms were sufficiently characteristic to point to a specific drug or one of a group as the offending agent.

The physician should never sign a death certificate or allow the release of the body to the undertaker if he is suspicious that the patient may have succumbed from poisoning, but should communicate with the coroner or medical examiner. If the patient is still living, and has been the victim of malicious poisoning, he should be removed from possible danger by transferring him to a hospital. The legal duties of the physician have then been fulfilled with the exception of any help which he may render the proper authorities on the basis of his contacts with the case.

Occurrence of Poisoning. Poisoning may be accidental, suicidal or criminal. Accidental poisonings are common in children. A young child especially conveys most objects to his mouth. The tragedy of the high incidence of poisonings in childhood is that most of them could be avoided. Parents cannot be too strongly urged to keep medicinals out of the reach of children. Neither should poisonous vermicides or insecticides be placed in the home. Many common household articles which are poisonous should be made unavailable to children. Accidental poisoning among adults is not uncommon and usually results from attempts at self-medication or from mistaking one drug for another.

Suicide by drugs and noxious gases is also common. Drugs have definite waves of popularity as suicidal agents. Barbiturates and carbon monoxide are two that are often employed. Every physician should be able to treat poisoning caused by agents commonly used for suicidal purposes.

Criminal poisoning was at one time much more prevalent than at present. The rapid strides made in the science of toxicology have largely discouraged this form of criminal attack.

Diagnosis of Poisoning. The diagnosis of poisoning is not simple. Although the toxic actions of most drugs are characteristic, there is scarcely a syndrome produced by a toxic agent which cannot be simulated by disease. For example, symptoms caused by the central nervous system stimulants may be mistaken for epilepsy, tetanus, hypoglycemic convulsions, etc.; those by the central nervous system depressants, for cerebral vascular accidents, uremic coma, brain tumor, etc. Special difficulty is experienced in diagnosing chronic poisoning. A significantly high percentage of individuals admitted to psychopathic institutions are found to be suffering from chronic bromide intoxication which often simulates a neuropsychiatric disorder. The true etiology of the symptoms of chronic acetanilid poisoning may escape all but the most astute observers. The more uncommon types of industrial poisoning may go undiagnosed until irreparable injury has been suffered by the patient.

There are a number of helpful signs and symptoms which assist in the detection of acute poisoning. The onset of illness is usually sudden and occurs in an individual who has been previously well. However, there are diseases which develop rapidly and a number of drugs which have a slow onset of action. Another factor suggestive of poisoning is that the symptoms usually follow the taking of food, drink or medicine. In the event that several individuals suffer from similar symptoms after partaking of the same food, the likelihood of a poisonous substance being the cause is great. Most often, however, it is the characteristic actions of a drug which are recognized. Many leave a tell-tale odor. Irritant drugs may produce their effects on the mucous membrane of the mouth and throat. Such drugs as atropine and morphine have characteristic actions on the pupil. The typical appearance of a person poisoned by carbon monoxide and the circumstances under which he is discovered immediately lead to an almost certain diagnosis. When all the factors of a case are considered the diagnosis of acute poisoning can usually be made with certainty. As a final check there are often simple chemical tests which can be performed rapidly in order to confirm the clinical diagnosis.

The diagnosis of chronic poisoning is often difficult. At times the symptoms and signs are not sufficiently specific to point to the toxic agent, and in many cases laboratory procedures are essential. In others, painstaking probing of the patient's history, habits, daily activities, working conditions, etc., may lead to a solution of the problem.

Treatment of Acute Poisoning. In the following discussion, only the general principles of the treatment of acute poisoning are discussed. The particular procedures employed in combating the effects of specific agents are presented under the individual drugs. Much can be learned from a general discussion, however, for in a number of instances it is not necessary to identify the specific substance causing symptoms in order rationally to treat a case of poisoning. Rather most emergency therapy is symptomatic. Success is often dependent upon celerity, and valuable time cannot be wasted in a positive identification of the specific cause of the patient's illness. The usual steps taken are (1) the removal of the poison from the body, (2) the administration of antidotes, and (3) supportive or symptomatic therapy. Although these procedures are listed in the order in which they are usually performed, there are times when it is necessary to give supportive or antidotal therapy before steps are taken for the removal of the poison.

Removal of Poison from Body. Poisons which have been applied externally are best removed by copious washing with water. If the toxic agent is a strong acid or base it is theoretically advantageous to wash with a dilute neutralizing agent. In actual practice, however, the loss of time in procuring the more suitable wash nullifies any theoretical advantage. In case the toxic agent is not water-soluble, a suitable organic solvent should be employed. For example phenol is best removed with alcohol or castor oil.

The removal of a poison that has been ingested orally is more difficult. A great deal of emphasis has been placed upon the use of *emetics*. Actually it is only in rare cases that such drugs are of any value. Emetics act by stimulating the medulla, either directly or reflexly by irritation of the walls of the stomach (page 812). Such medullary stimulation is followed by some degree of depression. Also, if the patient has ingested a central nervous system depressant, it is possible that either type of emetic may prove inactive. The administration of a medullary stimulant to an individual suffering from the effects of a central nervous system stimulant is likely to increase the severity of symptoms. A corrosive poison is in itself emetic. In the occasional instance in which the employment of an emetic is justified, the most useful drug is apomorphine. Apomorphine can be given parenterally, acts rapidly by a direct effect on the medulla, and is more certain in action than the gastric irritants which reflexly stimulate vomiting (page 813). Mustard is a common household article which has an emetic action and can be employed in an emergency (page 814).

Gastric lavage is a much more certain and thorough method for evacuating the stomach. The danger of perforating the esophagus or stomach in cases of corrosive poisoning or precipitating a convulsion in strychnine poisoning are the two major contraindications to this procedure. Once the stomach tube has been passed, the gastric contents can be evacuated and the stomach repeatedly washed in order to remove all traces of poison. Chemical antidotes may be employed in order to increase the efficiency of the lavage. Finally, after the stomach has been thoroughly cleansed and emptied, one can administer through the stomach tube a generous dose of a saline cathartic. This will speed the passage of any drug which has passed through the pyloric sphincter and thus diminish the extent of its absorption in the intestinal tract.

In using the stomach tube, care should be taken to prevent the aspiration into the lungs of gastric contents or lavage fluid. The head should be low and turned to the side when aspirating or siphoning material from the stomach. Also, when removing the tube from the stomach, it should be firmly pinched in order to forestall the possibility of fluid leaking and gaining access to the lungs as the opening passes the pharynx.

Inasmuch as many drugs are concentrated at the site of excretion, attention should be directed toward the organs for elimination of a particular poison. Although in most instances it is not possible markedly to hasten the excretion of a drug, precautions may be taken to protect the excretory organs. Large amounts of fluid should be given to dilute nephrotoxic poisons in the renal tubule. In a few instances the renal excretion of a drug can be enhanced by specific procedures. For example, in bromide poisoning, the excretion of bromide can be greatly hastened by the administration of chlorides. Water diuresis augments the excretion of sulfanilamide. It is only in isolated cases, however, that the renal excretion of a drug can be appreciably speeded. Volatile substances which are excreted by the lungs can be more rapidly eliminated by stimulating respiration, and for this purpose the inhalation of carbon dioxide is often employed. If the poison is excreted by the intestinal mucosa, care should be taken to avoid constipation.

Antidotes. Antidotes can be divided into two main classes, *chemical* and *physiological.* A chemical antidote is one which inactivates a poison by chemical means. The site of action of most chemical antidotes is the stomach where they precipitate, oxidize or otherwise render a drug innocuous or incapable of absorption. Usually the combination of antidote and drug is not a stable one and the gastric contents should be removed by lavage. A few chemical antidotes are given parenterally and can inactivate poisons that have already been absorbed. Outstanding examples are the use of sodium formaldehyde sulfoxylate in the treatment of mercury poisoning (page 734) and the employment of nitrites and thiosulfates for the treatment of cyanide poisoning (page 701). A physiological antidote is one which combats the physiological effects of a poison. An outstanding example is the use of stimulants of the central nervous system to overcome the effects of central depressants. Often one does not have a choice of antidotes but must resort to the one most readily available. The common household articles which are effective are milk and egg white for poisoning by heavy metals, flour and starch as colloidal substances to prevent absorption of all types of poisons, starch being particularly effective against iodine, and strong tea and diluted tincture of iodine for the precipitation of alkaloids. The specific antidotes employed against individual poisons are discussed throughout the text.

Supportive Therapy. Adequate supportive therapy is as important in the treatment of poisoning as is the administration of specific antidotes. It is important to maintain the vital processes of the body at the highest possible functional level in order to facilitate the detoxication and excretion of the poison and enable the patient to recover from the injurious effects. The patient should be kept in bed and warm, under competent surveillance, and particular attention should be paid to the respiration, circulation and organs of excretion and detoxication. This often necessitates hospitalization. Shock is a common symptom of acute poisoning and the routine of shock therapy (page 587) is often employed. The many drugs and the manner in which they are used to combat poisoning are discussed in the text.

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SECTION II

CENTRAL NERVOUS SYSTEM DEPRESSANTS

Drugs acting upon the central nervous system may be grouped into *stimulants* and *depressants.* The depressants are by far the more important, and represent the most widely used of all therapeutic agents. For convenience, central nervous system depressants may be divided arbitrarily into several categories. A simple and useful classification is as follows:

1. *General anesthetics,* such as ether, cyclopropane, ethylene.
2. *Sedative-hypnotic-soporific* drugs, such as the barbiturates, chloral hydrate, bromides.
3. *Narcotics,* such as morphine and related alkaloids.
4. *Analgesics* and *antipyretics,* such as the salicylates, acetanilid, aminopyrine.

It is evident that there is considerable overlapping in this classification. For example, any of the sedatives can be given in sufficient amount to cause anesthesia. Even such a mild sedative as bromide may cause profound coma if given in sufficiently large doses. On the other hand, the general anesthetics produce analgesia. From a therapeutic standpoint, however, the groups mentioned are fairly distinct.

The terms previously used may be more definitely delimited by the definitions which follow:

Anesthesia. Literally, this word means "without sensation." General anesthesia includes the loss not only of all modalities of sensation but also of consciousness. *Surgical anesthesia* is sufficiently deep to allow surgical operations to be performed. *Basal anesthesia* is a lighter degree of anesthesia obtained by the giving of sufficient preanesthetic medication. It allows the patient to be brought to the operating room in an unconscious state, yet not sufficiently depressed for surgical procedures. Tribromethanol is a good example of a basal anesthetic agent.

Narcosis. This term is variously defined. As used here, narcosis refers to a condition of analgesia accompanied by deep sleep or stupor. The action of a narcotic drug differs from that of an anesthetic in that pain is relieved before the occurrence of sleep or unconsciousness. Indeed, by administering a properly selected dose, analgesia may be obtained without stupefaction or sleep.

Hypnosis. In the pharmacological sense, hypnosis is a condition of sleep produced by somnifacient drugs. *Sedation* is a milder degree of hypnosis in which the patient is awake but calmed.

Analgesia. This term refers to the obtundation of pain. An analgesic differs from a narcotic in that it characteristically relieves pain without producing stupefaction or unconsciousness.

CHAPTER 2

HISTORY AND THEORIES OF GENERAL ANESTHESIA

HISTORY OF SURGICAL ANESTHESIA

The earliest use of anesthetic agents is lost in antiquity. The Egyptians, who widely practiced surgery, probably had narcotics of various sorts. The Chinese employed hashish (cannabis indica) for its analgesic properties. Pliny, Dioscorides and Apuleius recommended Mandragora (belladonna alkaloids) for use before operations. In addition to drugs, many bizarre and cruel physical methods were devised to render patients temporarily unconscious. For example, the Assyrians asphyxiated children by strangulation before circumcision, a practice used in Italy as late as the 17th century. Cerebral concussion, produced by striking a wooden bowl placed on the head, was also employed.

For many centuries morphine, hyoscine and alcoholic beverages were the main drugs used to ease the pain of surgery. The use of anesthetics for complete and safe abolition of pain in surgical operations is an accomplishment especially of an epoch-making five year period between 1842 and 1847. Before the time of anesthesia, operations were horrible ordeals and the surgeon attempted to shorten the agony by working with great haste. Amputations, for example, were completed in a few seconds and surgeons boasted of their speed. Obviously, careful surgery and delicate treatment of tissues were impossible.

The first gas anesthetic to be discovered was nitrous oxide, by Priestley in 1776. In 1799, Sir Humphry Davy announced that this gas had the ability to destroy pain and suggested its use during surgical operations. For forty-three years this suggestion lay unheeded.

The discovery of surgical anesthesia was an American contribution. Crawford W. Long of Athens, Georgia, had a patient inhale ether while he removed a small tumor from the neck. The subject felt no pain. This was in March, 1842, over three centuries after the chemical discovery of the compound by Valerius Cordus in 1540. Pearson in 1795 had recorded the use of ether inhalations to control the pain of colic, and Beddoes in the next year published a case report of deep sleep induced by ether. American physicians were familiar with the effects of ether due chiefly to Faraday, who had written about the stupefying effects of the compound as early as 1818, as follows, "When the vapor of ether mixed with common air is inhaled, it produces effects similar to those occasioned by nitrous oxide." Nevertheless, in conservative medical circles, ether was considered to be dangerous in amounts which caused loss of consciousness. Medical students in Athens, Georgia, had experimented with Faraday's observation by holding ether parties, or "jags" as they were called. On one occasion they unexpectedly anesthetized a young boy very deeply. Dr. Long often was a leader in these ether frolics, having first witnessed them in Philadelphia several years before, and he became greatly interested in the possibilities of ether as an anesthetic. Finally, he used it for anesthesia on several occasions in his surgical practice. Unfortunately, Long failed adequately to publish his experiences, and his findings remained unknown until ether anesthesia was rediscovered and properly developed by Morton and others, and used as an accepted procedure in surgery.

At this point the history of anesthesia once again reverts to nitrous oxide. In the early 1840's, a peripatetic chemist-lecturer by the name of Colton traveled through New England giving public demonstrations of nitrous oxide or "laughing gas" inhalation for an admission charge of 25 cents. On December 10, 1844, he arrived in Hartford, Connecticut. The newspaper advertisement promised that he would allow volunteers to inhale the gas, and that eight strong men would occupy the front seats to protect those under the influence of the gas from injuring themselves or others. Horace Wells, a dentist in

Hartford, attended the lecture. A person named Cooley volunteered to inhale the gas, and during the inhalation became dazed and belligerent. He jumped from the stage to fight with one of the "strong men" in the front row, but the latter fled. After him went Cooley, who during the chase jumped over a chair, tripped and fell to the ground. The fall brought him to his senses and he returned to his seat sobered and apologetic. Suddenly he noticed that his leg was gashed and bleeding where he had struck the chair during the chase. He was astonished by the presence of the wound for he had experienced no pain. Wells carefully questioned him regarding this, but he insisted that there had been no pain with the injury. The very next day, Wells had one of his teeth extracted painlessly under nitrous oxide, Colton administering the gas. He then used nitrous oxide in his dental practice in Hartford and gave the matter unrestricted publicity.

In January, 1845, Wells went to the Massachusetts General Hospital in Boston to exhibit his gas. The demonstration unfortunately failed, the patient awaking too soon and screaming in pain. Wells met with unjust ridicule because it was not then appreciated that the gas is hard to administer. The wonder is that without special apparatus Wells was successful at all. He was unaware of the deeper degree of anesthesia obtainable with nitrous oxide.

The introduction of ether in the following year placed Wells and nitrous oxide in the background. Greatly embittered, Wells became insane and finally committed suicide. Wells must be given credit for appreciating the importance of nitrous oxide anesthesia and attempting to apply it in dental surgery. In the early 1860's, Colton, the traveling lecturer who 20 years before had by his demonstration initiated the work of Wells, revived the use of nitrous oxide and in a few years the gas was extensively employed in dentistry.

The story meanwhile returns to ether. William T. G. Morton of Boston was a former dental associate of Wells and much interested in nitrous oxide anesthesia. He was also acquainted with the stupefying effects of ether. Morton entered the Harvard Medical School as a student and continued his practice of dentistry in order to defray his expenses. He consulted Prof. Charles T. Jackson, his chemistry teacher, concerning the problem of anesthesia. It is said that Jackson had previously accidentally anesthetized himself and a pharmacist named Burnell into a deep stupor while they were playing cards near a tea kettle, the lamp of which was filled with ether instead of alcohol. Another version is that Jackson accidentally anesthetized himself with ether while inhaling the vapor as an antidote for chlorine gas, of which he breathed too much during a chemistry demonstration before his students. Morton apparently learned from Jackson that ether, to be useful, should be pure sulfuric ether, the kind that Burnell sold. Morton then practiced on himself, the family dog, cats, hens and rats, and finally successfully extracted a tooth under ether September 30, 1846. Soon he asked Dr. J. C. Warren, Professor of Surgery at Harvard Medical School, for permission to make a test trial of ether in a surgical operation. The request was allowed and the day set for the demonstration was October 16, 1846.

The story of this classic demonstration has been retold countless times. The operating room at the Massachusetts General Hospital remains as a memorial to the first public demonstration of surgical anesthesia. In the gallery of this room skeptical spectators gathered, for the news had spread that a second year medical student had developed a method for abolishing surgical pain. The patient was brought in and Doctor Warren, the surgeon, waited in formal morning clothes for gowns, masks, gloves, surgical asepsis and the bacterial origin of infection were entirely unknown in that day. Everyone was ready and waiting, even the strong men to hold down the struggling patient, but Morton did not appear. Fifteen minutes passed, and the surgeon, becoming impatient, took his scalpel and turning to the gallery said, "As Doctor Morton has not arrived, I presume he is otherwise engaged." While the audience smiled and the patient cringed, the surgeon turned to make his incision. Just then Morton entered, his tardiness being due to the necessity for completing an apparatus with which to administer the ether. It is told that Doctor Warren stepped back, and pointing to the man strapped to the operating table said, "Well, sir, your patient is ready." Surrounded by a silent and unsympathetic audience, Morton went quietly to work. After a few minutes of ether inhalation, the patient was unconscious whereupon Morton looked up and said, "Doctor Warren, *your* patient is ready." To this day, anesthetists often inform the surgeon when to start operating by saying, "Doctor, your patient is ready." The operation was begun. The patient gave no sign of pain, yet he was alive and breathing. The strong men were not needed. When the operation was completed, Doctor Warren turned to the astonished audience and said, "Gentlemen, this is no humbug." Dr. Henry J. Bigelow, an eminent surgeon attending the demonstration, remarked, "I have seen something today that will go around the world."

The complete success of this demonstration resulted, after a short initial period of disbelief, doubt and delay, in the rapid introduction of general anesthesia for surgical operations. Dr. Warren wrote, "A new era has opened on the operating surgeon. Who could have imagined that drawing a knife over the delicate skin of the face might produce a sensation of unmixed delight? That the contorting of an ankylosed joint should coexist with a celestial vision? If Ambroise Paré, and Louis, and Desault, and Chesselden and Hunter, and Cooper, could see what our eyes daily witness, how would they long to come among us and perform their exploits once more. And with what fresh vigor does the living surgeon, who is ready to resign the scalpel, grasp it, and wish again to go through his career under the new auspices." Dr. Oliver Wendell Holmes, in addressing his medical class in the fall of 1847, said, "The knife is searching for disease—the pulleys are dragging back dislocated limbs—Nature herself is working out the primal curse which doomed the tenderest of her creatures to the sharpest of her trials, but the fierce extremity of suffering has been steeped in the waters of forgetfulness, and the deepest furrow in the knotted brow of agony has been smoothed forever."

The sequel to the story is an unhappy one. Morton obtained a government patent in 1846. This act and the allegedly unethical methods he used to obtain his patent raised a storm of protest, into which Jackson, Long, and Wells entered as parties in the contest for priority. Wells became insane and committed suicide; Jackson became insane; and Morton, embittered, impoverished and unhappy, died of apoplexy. A monument erected by the citizens of Boston over the grave of Dr. Morton in Mt. Auburn Cemetery near Boston bears the following inscription written by Dr. Jacob Bigelow:

WILLIAM T. G. MORTON

Inventor and Revealer of Anaesthetic Inhalation.
Before Whom, in All Time, Surgery Was Agony.
By Whom Pain in Surgery Was Averted and Annulled.
Since Whom Science Has Control of Pain.

The search for other anesthetics was soon under way. Chloroform had been discovered in 1831, and 16 years later it was tried on animals by Flourens. In the same year (1847), a surgeon in Edinburgh by the name of Simpson successfully tried chloroform anesthesia in man. The suggestion to do so was made to Simpson by McWaldie. The story goes that during the first demonstration the attendant dropped and broke the bottle containing the chloroform. Inasmuch as there was no more immediately available, the operation was undertaken without anesthesia and the patient died almost with the first stroke of the knife. If this death had occurred while the chloroform was being used, it might have postponed the introduction of anesthesia in England for many years.

Strong opposition sprang up against the use of anesthesia in surgery and particularly its employment during childbirth. This opposition came especially from church circles. Simpson effectively met the not unexpected attack by pointing out that God, the first surgeon, had used anesthesia by causing a deep sleep to fall upon Adam while He removed the rib from which Eve was made. Simpson was knighted for his contribution by Queen Victoria, whom chloroform protected from many a labor pain. Chloroform, despite its inferiority to ether, remained the favorite anesthetic in Europe until comparatively recent times.

During the early years of the use of anesthesia, surgeons and nurses did not use the word "anesthesia"; the experience was a new one and there was no expression to describe it. Oliver Wendell Holmes later introduced the words *anesthesia, anesthetic* and *anesthetist.* The following letter was written by Holmes to Morton:

Boston, November 21, 1846.

My dear Sir: Everybody wants to have a hand in a great discovery. All I will do is to give you a hint or two, as to names, or the name, to be applied to the state produced and the agent.

The state should, I think, be called "anaesthesia." This signifies insensibility, more particularly (as used by Linnaeus and Cullen) to objects of touch. (See Good-Nosology," p. 259). The adjective will be "anaesthetic."

Thus we might say the state of anaesthesia, or the anaesthetic state . . . I would have a name pretty soon, and consult some accomplished scholar such as President Everett, or Dr. Bigelow, Sr., before fixing upon the terms, *which will be repeated by the tongues of every civilized race of mankind. . . .*

You could mention these words which I suggest for their consideration; but there may be others more appropriate and agreeable.

Yours respectfully,
O. W. Holmes

It was also Holmes who, when asked to decide whether Morton or another was the discoverer of ether so that the name might be carved on a monument to be dedicated for the purpose, evaded the ticklish question by saying, "Gentlemen, I propose that this monument be dedicated to ether." His true opinion, however, is revealed in the following statement from a letter written years later, on April 2, 1893, to Edward Snell: "Both these gentlemen (Jackson and Wells) deserve 'honorable mention' in connection with the discovery, but I have never a moment hesitated in awarding the essential credit of the great achievement to Dr. Morton." Dr. William H. Welch voiced a similar sentiment when he wrote as follows, ". . . we need not in this instance withhold from Dr. Long the credit of independent and prior experiment and discovery, but we cannot assign to him any influence upon the historical development of our knowledge of surgical anesthesia or any share in the introduction to the world at large of the blessings of this matchless discovery." And again, ". . . in my judgment, after careful study of the evidence, the greater share of the honor belongs to Morton. This was the prevailing opinion of those most competent to judge and best acquainted with the facts of the time. . . ." Perhaps James T. Flexner has aptly summarized the problem by stating that certainly there is enough credit in the discovery of anesthesia for two to share it.

Regardless of the relative merits of the various contestants in the "ether controversy" for priority of discovery, the significance of the "death of pain" resulting from the introduction of surgical anesthesia has been beautifully described by the poet-physician Weir Mitchell, at the semi-centennial anniversary of anesthesia:

Whatever triumphs still shall hold the mind,
Whatever gift shall yet enrich mankind,
Ah! here no hour shall strike through all the years,
No hour as sweet, as when hope, doubt, and fears,
'Mid deepening stillness, watched one eager brain,
With Godlike will, decree the Death of Pain.

THEORIES CONCERNING THE MECHANISM OF ACTION OF ANESTHETICS

The mechanism by which anesthetics depress the activity of the central nervous system is poorly understood. Despite the large amount of investigative work on the subject, the explanations are as yet hypothetical. Many advances have occurred which allow a clearer picture of the mechanism of formation and transmission of the nerve impulse in the peripheral autonomic and somatic nervous systems. Information concerning chemical mediation of stimuli, the rôle of potassium in nervous activity, and the metabolic activity of nerve fibers is not as yet transferable to inhibitory or excitatory processes in the central gray matter. Indeed, the metabolic activity of the brain differs from peripheral nerves in important respects. Even the fundamental mechanisms underlying such a physiological occurrence as normal sleep are obscure. Because of the paucity of conclusive information, the following discussion of the theories of anesthesia will be brief. It should be noted in passing that this lack of knowledge has not interfered seriously with the clinical use of anesthetics or the continuous improvement in anesthetic agents and technics of anesthesia.

There are many agents, physical and chemical, which are capable of producing depression of the central nervous system. Cold, fatigue, oxygen lack, and certain ions (Br, Mg, etc.) are but a few of these. Clinical anesthesia is obtained especially by the use of the hydrocarbons of the methane series. A number of alkaloids also cause marked central depression. It is difficult, therefore, to believe that a single mechanism underlies the action of all these diverse agents. Nevertheless, numerous investigators have sought a unitary explanation by a study of the correlation between physical and chemical properties of drugs and their anesthetic potency. The result of most of this work has been the finding that numerous anesthetic agents show affinities for lipids and for cell surfaces. In some instances, these affinities appear to be quantitatively related to anesthetic strength. Two theories of anesthesia have developed from the knowledge of these affinities, the one usually termed the *"Meyer-Overton law"* and the other known as the *surface tension* *or adsorption theory.* In addition to these two hypotheses, several other explanations of anesthesia exist. For a review of the pertinent literature, the reader is referred to Henderson (1930), Clark (1937), Meyer (1937) and Beecher (1938).

Lipoid Theory. The lipoid theory was advanced by Meyer (1899, 1901). In its simplest terms, it states that there is a direct parallelism between affinity of an anesthetic for lipid and its depressant action. In other words, the more soluble an agent is in oil and the less soluble in water, the more anesthetic it will prove to be. This concept has been formulated as a ratio known as the oil:water partition coefficient and expressed by $\frac{\text{solubility in fat } (S_f)}{\text{solubility in water } (S_w)}$. The higher the coefficient, the more powerful is the anesthetic. Inasmuch as nerve cells and their membranes contain lipids, the anesthetic is thought to gain access to nerve tissue by virtue of its lipid solubility. Changes in cell membrane permeability and in electrical polarization of cells may then occur and in this manner depress reception or discharge of impulses. Evidence for the lipoid theory rests mainly on the fact that the arrangement of a series of chemical agents according to their solubility coefficients agrees fairly well with the order obtained by grouping the same substances according to their anesthetic potency. The many arguments against the theory cannot be given at length but mainly center around the facts that most of the solubilities have been studied *in vitro* with vegetable oils and water rather than with brain lipids and body fluids; that a number of anesthetics fall out of line, notably chloral hydrate; that alkaloids and inorganic ions do not comply with the theory; and that many fat-soluble substances closely related to the anesthetics have no depressant action on the nervous system. In summary, it may be stated that the Meyer-Overton theory points out an interesting analogy which in some way may be concerned with the phenomenon of central nervous system depression.

Surface Tension or Adsorption Theory. This theory was proposed especially by Traube (1904), Lillie (1909) and Warburg (1921, 1930). It relates the potency of anesthetics to their ability to lower surface tension. This property of anesthetics may account for the accumulation of drugs on cell surfaces, but does not explain their depressant action. It is assumed that the physical presence of the chemical in some way alters the surface properties and hence permeability of nerve cells, or interferes with cellular metabolic processes.

Cell Permeability Theory. This theory, advanced particularly by Höber (1907), Lillie (1909, *et seq.*) and Winterstein (1915, 1916), is an extension of the adsorption theory. It holds that adsorbed anesthetics cause a change in the permeability of the cells of the central nervous system. Permeability is decreased by the anesthetic agent whereas stimulation of nerve cells has the opposite effect. The mechanism by which permeability is affected by depressant drugs is thought by Höber and Lillie to be due to the alteration produced in the state of the lipids in the cell membrane. Polarization studies by Spiegel and Spiegel-Adolf (1938) are interesting in this connection and indicate that ether, chloroform, chloral hydrate, phenobarbital, and dial increase the density of the cellular surface films in the cerebral cortex and brain stem.

Colloid Theory. This concept was advanced by Claude Bernard (1875) and elaborated by Bancroft and Richter (1931). The theory holds that an aggregation of cell colloids causes or accompanies anesthesia and that the process is reversible, thereby allowing for recovery. The experimental evidence for the theory is not all that is to be desired.

Inhibition of Oxidation. This theory has not yet been entirely formulated, but evidence being accumulated by cell physiologists and enzyme chemists seems to indicate that certain anesthetics produce central depression or narcosis as a result of interference with the enzymatic components of the respiratory system of nerve cells and the inhibition of the oxidation of glucose by the brain. Most of this work has been performed *in vitro* on cortical tissue slices. For example, Quastel and associates (1932, *et seq.*) have shown that the respiration of slices of rat brain cortex is not inhibited by certain barbiturates or ether in the absence of glucose but is markedly reduced in the presence of glucose by concentrations of the drugs which produce anesthesia in the intact animal. Although the *in vitro* experiments of Jowett (1938) would appear to indicate that ether and alcohol differ from certain other agents in requiring somewhat higher concentrations to inhibit oxidation of glucose than are necessary for clinical anesthesia, nevertheless it is probable that the specific inhibitory effects of anesthetic drugs on glucose metabolism in the brain are related closely to the phenomenon of anesthesia. Many anesthetics, in concentrations employed clinically, greatly inhibit oxidation by brain tissue of glucose, lactate and pyruvate. The inhibition is steady and reversible, related to the concentration of anesthetic, and particularly marked for the pyruvic acid oxidizing system. It is suggested that there is a factor or dehydrogenase in brain highly sensitive to anesthetics which acts as a hydrogen carrier in tissue respiration between pyruvic dehydrogenase and cytochrome oxidase.

Electrical Theory of Anesthesia. Studies of the action potentials of the brain during anesthesia produced by various central nervous system depressants have led some investigators to suggest that anesthesia is due to a decreased negative potential of the cerebral cortex and lessened conductivity through the cerebrospinal axis. The theory, however, is more descriptive than explanatory. To cite but two examples of work in this field, lighter grades of anesthesia (produced by avertin or barbiturates) cause changes in the cortical action potentials similar to those observed during normal sleep. Ether and chloroform produce marked reduction in both the voltage and frequency of the action potentials. (*See* Burge and associates, 1936; Derbyshire and coworkers, 1936; Bremer, 1936; Gibbs and associates, 1937; Forbes and Morison, 1939.)

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CHAPTER 3

STAGES OF ANESTHESIA

The *stages of anesthesia* can best be understood by first appreciating the pattern of action of the general anesthetics. This pattern consists of an *irregularly descending paralysis of the central nervous system.* The term "irregularly" is used in the anatomical sense, and refers to the fact that in the course of descending paralysis the medulla is temporarily spared. Thus, the general anesthetics first depress the cortex, then the basal ganglia and cerebellum, and next the spinal cord. First the sensory and then the motor functions of the cord are affected, probably from below upward. Lastly, the medulla, which apparently is more resistant to anesthetics, is involved, and paralysis of the vital respiratory and vasomotor centers is the usual cause of death from toxic concentrations. It is evident that the most highly developed functions of the nervous system are depressed first, and the phylogenetically oldest functions last. If this anatomical scheme is kept in mind, the signs and symptoms of the several stages of anesthesia will be understood more readily.

Although the divisions are somewhat arbitrary, the stages of anesthesia are four in number as follows:

I. *Stage of Analgesia or Altered Consciousness.* This is the stage corresponding to the action of the anesthetic agent on the higher cortical centers.

II. *Stage of Delirium or Excitement.* This is the stage resulting from the depressant action of the anesthetic on higher motor centers, with a consequent release of automatic lower motor mechanisms. The patient is unconscious in this stage, and hence there are no subjective symptoms. The first two stages comprise what is termed the *induction period.*

III. *Stage of Surgical Anesthesia.* This is the stage during which the action of the anesthetic agent is manifested on the spinal cord. Sensation and spinal reflexes are abolished and muscular relaxation is obtained.

IV. *Stage of Medullary Paralysis.* This is the stage corresponding to the paralytic action of the anesthetic on the vital functions of the medulla and brain stem. It must be carefully guarded against because respiratory failure and vasomotor collapse ensue and rapidly lead to death.

The stages of anesthesia vary somewhat in character and duration, depending upon the type and concentration of the agent used, the speed of induction and the skill of the anesthetist. For example, with ether and chloroform, the traditional stages are usually clearly seen. With ethylene, divinyl ether and cyclopropane, however, induction is more rapid and hence the stages are less clearly defined. When anesthesia is produced by the intravenous injection of barbiturates, unconsciousness occurs within a few seconds so that surgical anesthesia supervenes almost immediately.

The *relative* duration of the stages is constant with all of the volatile anesthetic agents, but the time necessary to reach medullary paralysis varies greatly with different anesthetics. This time is approximately as follows (Guedel, 1937):

Ether	10 to 30 min.	Ethylene	1 to 4 min.
Chloroform	4 to 12 min.	Ethyl chloride	1 to 4 min.
Nitrous oxide	1 to 4 min.	Cyclopropane	½ to 3 min.

The *signs and symptoms* of the four stages of anesthesia may now be described in detail. Significant variations from the usual pattern will be discussed under the pharmacology of the individual anesthetics. The following discussion refers especially to the inhalation anesthetics, and particularly to ether and chloroform.

First Stage: The Stage of Analgesia or Altered Consciousness. The first stage lasts from the first inhalation of the anesthetic until consciousness is lost. It should constantly be remembered by the surgeon, assistants and anesthetist that the patient is still conscious and care should be taken as to what is said and done in his presence. For example, the patient should not be strapped to the table in this stage, nor should the serious nature of his illness be discussed.

Subjective Symptoms. The patient quickly experiences a feeling of warmth which extends over his entire body. A sensation of suffocation, noted particularly with ether, also occurs and is quite unpleasant. It is not due to asphyxia but to the anesthetic agent. Local irritant effects from the vapor or gas may cause smarting of the nose, throat and eyes. As a result of this irritation, lacrimation, salivation and excess secretion of mucus occur unless atropine has been given. Suffocative or irritant sensations may cause the patient to struggle, to breathe irregularly or to hold his breath. This can be prevented by gentle induction and by attempting to get the patient to cooperate. This latter is often done by having the patient inhale in response to the counting or command of the anesthetist.

After the first few deep inhalations, sensations gradually become dulled and abnormal. Soon the body feels stiff, unmanageable, or peculiarly buoyant. Some patients feel as if they were being hurled through space. Thoughts are blurred and uncontrollable, and articulation becomes difficult and indistinct. Hallucinations are not infrequent; the patient often hears loud noises or a buzzing sound, and he may see bright lights. Analgesia gradually ensues with obtundation of the senses of pain and touch. Late in this stage a scalpel incision is perceived as though a blunt instrument were drawn across the skin. Numbness and loss of sensation occur earliest in the skin of the back and extremities. This spreads to the genitalia, then over the rest of the body and finally involves the peripheral sensory distribution of the cranial nerves. Pain is totally abolished just before the onset of unconsciousness.

Sensory functions of both the cerebral cortex and spinal medulla disappear earlier than the motor functions. Experimental evidence shows that sensory cells and synapses are paralyzed before motor units. Surgical procedures cannot be undertaken until the motor components of reflex arcs are sufficiently depressed to allow muscular relaxation.

Objective Signs. During stage I, the skin of the face and neck is flushed. The pupils are normal in size but dilate as the patient begins to pass into the second stage. The pulse is somewhat rapid and the blood pressure may be elevated, mainly from excitement. Study has shown that a rise in blood pressure is often present even before the induction and may amount to from 20 to 100 mm of mercury. Respiration may be increased in rate and irregular, or the breath may be held if the anesthetic is irritating. It is important to have the patient cooperate in keeping the rate and depth of respiration even. The superficial and deep reflexes are intact.

Second Stage: Stage of Delirium or Excitement. This stage extends from the onset of unconsciousness to the beginning of surgical anesthesia. It may be entirely absent, especially in young children. The patient should now be strapped to the operating table, but preparation of the operative field is further delayed because such stimuli may exaggerate the excitement.

Objective Signs. In this stage, the eyes close, the jaws become set and muscular tonus increases. Excitement and marked involuntary motor activity may occur at this time, due to paralysis of the higher motor centers and the consequent release of lower reflex motor mechanisms. The patient may laugh, shout, sing, swear and thrash about. The character of the excitement varies with the speed of induction and the personality of the patient. Delirium is more likely to occur in patients with elevated metabolic rates or in alcoholics.

The *respirations* are likely to be irregular and respiratory reflexes exaggerated. This constitutes one of the greatest dangers of surgical anesthesia, and makes the second stage the one to be most carefully handled. Inasmuch as the patient is unconscious and can no longer cooperate, respiratory reflexes elicited by irritating anesthetic vapors cause spasmodic inspiratory or expiratory arrest, coughing, or alternating periods of shallow and deep breathing. The respiratory irregularities result in an uneven rate of absorption of the anesthetic into the blood stream. After a period of apnea, the patient usually breathes deeply and rapidly and a dangerously high concentration of anesthetic may be quickly reached in the blood. The danger is particularly great with chloroform, a sudden high concentration of which in the coronary circulation may result in ventricular fibrillation and death. The secretion of epinephrine consequent upon painful stimulation from premature operative procedures contributes to the likelihood of such ventricular fibrillation, and therefore operations in this stage of partial anesthesia are particularly dangerous and should be strictly avoided. Most anesthetic deaths occur during the second stage.

It is therefore important that stage II be conducted smoothly. If the induction is stormy, the entire period of surgical anesthesia may be irregular and troublesome. If the character of the respirations permits, the patient should be hurried through the second stage in order quickly to pass the danger period. If the patient holds his breath, the anesthesia should be lightened or the mask removed, so that when respirations are resumed a large amount of anesthetic vapor is not inhaled. Under no circumstances should the anesthesia be crowded if the breath is held. At the end of the second stage, respirations again become regular and deep.

Respiratory Arrest During the Induction Period. There are two types of respiratory arrest occurring in the induction period which are quite different from the reflex apnea arising from concentrated irritant vapors. One is the result of excessive preanesthetic medication, and the other is due to an overdose of the anesthetic (Haggard, 1924; Guedel, 1937). Ordinarily, the threshold for stimulation of the respiratory center is adjusted at the level of the normal CO_2 concentration of the blood. In both types of respiratory arrest, there is a disproportion between the respiratory threshold and the CO_2 level in the tissues.

(1) *Respiratory cessation due to overdose of preanesthetic morphine.* If a patient has received too much opiate, the respiratory minute volume is considerably lowered, and the medullary center is relatively insensitive to the CO_2 level of the blood, despite the fact that the latter may be above normal as a result of the respiratory depression. If hyperpnea develops during induction of anesthesia, as often occurs with the use of the ether open drop method, the CO_2 content of the blood drops much below the threshold of the depressed respiratory center, and respiration ceases when consciousness is lost. Even if breathing does not stop completely, the effective respiratory exchange is insufficient to allow enough ether to be carried from the lungs into the blood, and surgical anesthesia

does not occur. When anesthesia is administered by a closed system, this sequence of events can be avoided because the CO_2 content of the inspired air can be controlled and raised until there is a high enough level in the blood to stimulate respiration. At the termination of anesthesia, during which an elevated concentration of CO_2 has been inhaled, the CO_2 should not be withdrawn suddenly because the abrupt decrease in the blood concentration of the gas may precipitate apnea. Carbon dioxide and oxygen should be given until sufficient anesthetic or opiate has been eliminated to lower the threshold of the respiratory center to the point where the physiological concentration of CO_2 is again effective.

(2) *Respiratory cessation due to overdose of anesthetic agent.* This type of apnea occurs most frequently in apprehensive children who have had insufficient preoperative preparation or medication, and who are given open ether anesthesia by an unskilled anesthetist. Two factors contribute especially to the arrest of breathing. First, the frightened child struggles and cries when the administration of anesthetic is started. Crying causes CO_2 to be blown off and thus diminishes the concentration in the blood of this chemical stimulus to the respiratory center. Second, the ether is usually pushed in an attempt to "rush through the excitement period." Hyperpnea induced by fright causes the concentrated ether vapor to be carried quite rapidly into the lungs, blood and brain. In this way, the central nervous system, because of its large blood supply, is flooded with ether and the threshold of excitability of the respiratory center is elevated. The two factors, a relatively insensitive medulla and a lowered CO_2 content of the blood, combine to stop respiration. The child quickly becomes cyanotic after depletion of the oxygen reserve and the pupils dilate widely. Artificial respiration restores the patient to normal rapidly. The patient is not a poor risk and the operation need not be postponed. Breathing would eventually start spontaneously even without artificial respiration. The circulation, still unimpaired, would soon carry the ether from the flooded brain to other tissues which have lower concentrations of the anesthetic. The CO_2, which accumulates as a result of the apnea, combined with the decreasing depression of the medullary centers, as the ether concentration falls, reinitiate spontaneous breathing. Artificial respiration, however, should always be performed when respiration ceases.

Vomiting and retching may occur, especially if the patient is held in stage II. Premonitory swallowing often heralds the approach of emesis. The patient's head must immediately be lowered and turned to one side, or aspiration of vomitus into the respiratory tract may occur. This unfortunate accident may result either in pneumonia which may prove fatal or in asphyxia from obstruction of the larynx or trachea by food particles. Vomiting rarely attends the use of the rapidly acting anesthetics, apparently because the stage of irritability of the vomiting center is too quickly passed.

Analgesia is present during the second stage but spinal reflexes are still active. Consequently muscular relaxation is insufficient for any but the most superficial operations. Painful procedures are dangerous because the response to such stimulation (including incidental dreams) is exaggerated and may lead to violent physical activity. Bodily injury may result.

The *pupils* which begin to widen at the beginning of the second stage remain dilated until the patient enters the third stage, at which time they contract to a smaller size than normal. The pupillary dilatation of stage II is reflex in nature in contrast to the paralytic dilatation of stage IV. The pupillary reflexes to light are still present in the second stage.

The *skin color* varies with the anesthetic used. It is usually red when ether is used, but may be gray or pale with chloroform. The *pulse* is accelerated, and the blood pressure elevated. All superficial and deep *reflexes* are present.

The proper management of the second stage of anesthesia consists essentially in the restraint of the patient, avoidance of exciting stimuli, and rapid induction. Correct preanesthetic medication is important in insuring against accidents during this stage.

Third Stage: Surgical Anesthesia. Stage III extends from the end of the second stage until paralysis of the medulla and respiratory arrest occur. The onset of surgical anesthesia is not sharply demarcated but the following signs are helpful. (1) The respiratory irregularity of the second stage disappears. (2) The dilated pupils begin to constrict. (3) If the anesthetist suddenly increases the concentration of anesthetic vapor, reflex respiratory arrest and swallowing no longer occur, whereas both of these reflex responses to concentrated vapor can be elicited during the second stage. (4) The eyelid and conjunctival reflexes are now absent. (5) Roving movements of the eyeballs are characteristic of early stage III.

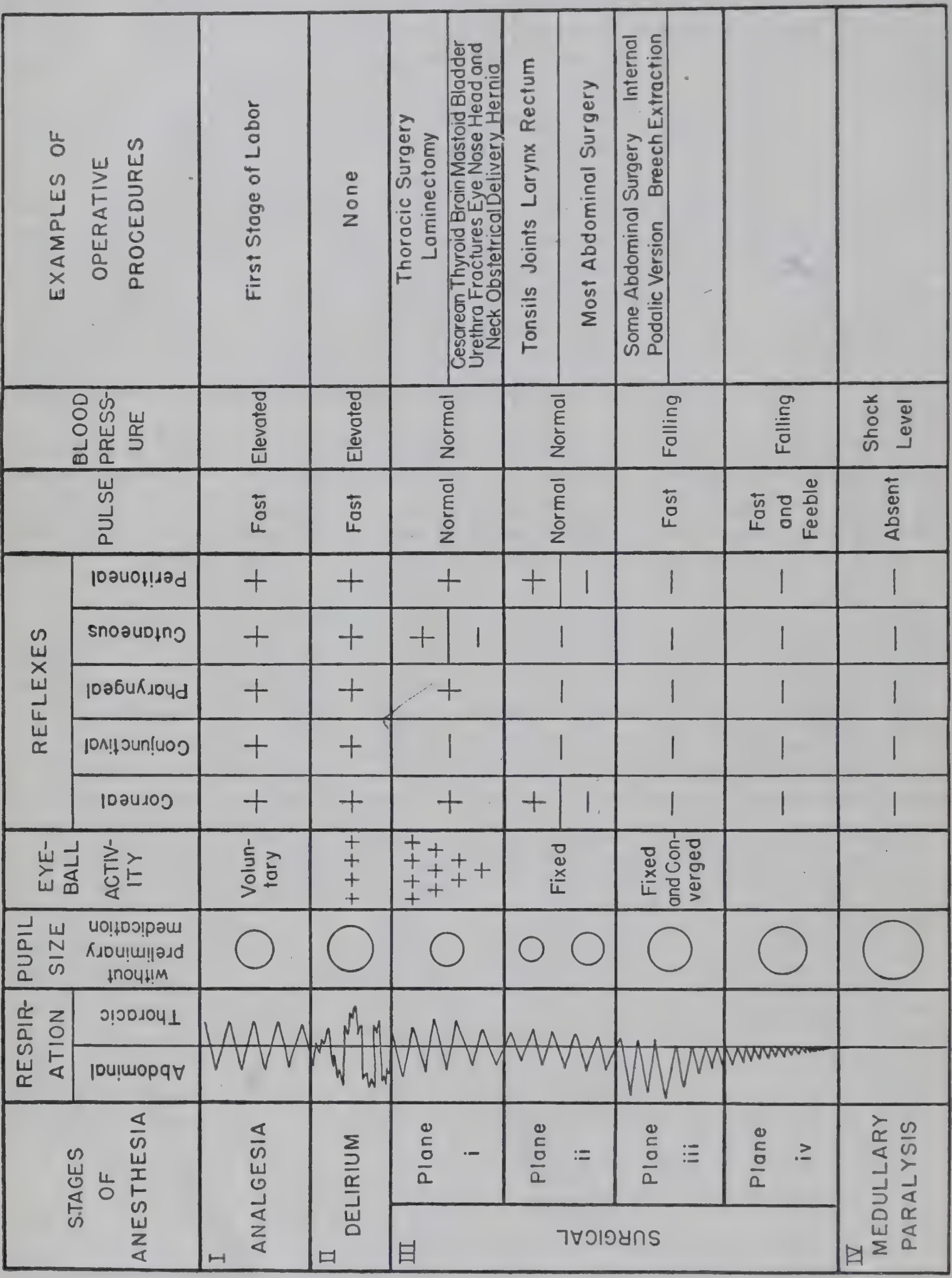
Planes of Anesthesia. The *physical signs* during surgical anesthesia depend on the plane of anesthesia. The third stage is divided into four planes, numbered from i to iv (Guedel, 1937). This division may be simplified by remembering that plane i represents the very onset of stage III, suitable for the simpler operations; planes ii and iii comprise the depths of anesthesia required for most major surgery, while plane iv represents the onset of bulbar paralysis as indicated by respiratory arrest. The major differences in physical signs in the various planes are (1) the character of the respiration, (2) the character of the eyeball movements, and (3) the size of the pupils. Unfortunately, pupillary size is not often helpful because morphine and atropine are usually administered prior to anesthesia.

The usefulness of the above physical signs in judging the depth of anesthesia can be seen from studying Figure 3, and may be illustrated by a few examples. (1) Full and regular respirations, which are both abdominal and thoracic in character, associated with roving eyeballs, inform the anesthetist that the patient is still in plane i. (2) When the regular respirations coincide with fixed eyeballs, the anesthetist knows that the depth of anesthesia has reached plane ii. (3) The beginning of plane iii is indicated by increased abdominal respirations and delayed thoracic inspiratory effort which herald the beginning paralysis of the intercostal muscles. Also at this plane of anesthesia the eyes become fixed in the converged position. The diaphragm compensates for decreased thoracic activity and the increasing downward excursions of the diaphragm during inspiration become more and more noticeable as plane iii advances. The resulting movements of the abdominal viscera may be extremely annoying to the surgeon during an abdominal operation. (4) The transition between the lower half of plane iii and plane iv is marked by complete intercostal paralysis. The patient is never allowed to pass beyond plane iii. (5) Complete cessation of all respiration marks the passage from plane iv of stage III to stage IV.

Respiration. During the major part of surgical anesthesia, respirations are full and regular, somewhat slowed as in physiological sleep, and are often stertorous. This is due to the relaxation of the muscles of the pharyngeal wall with the result that the soft palate vibrates with the respiratory cycle. In planes i and ii, ether, ethyl chloride, divinyl ether and chloroform stimulate respiration, the relative intensity of stimulation being in the order named. The respiratory volume is increased about 25 per cent above normal. In lower plane ii, the agents mentioned begin to depress respiration in the reverse order. Nitrous oxide and ethylene stimulate respiration throughout anesthesia, and do not become depressants by their own action. With these two anesthetics, coincident mild anoxemia stimulates respiration but severe anoxemia depresses it. Cyclopropane neither stimulates nor depresses breathing until plane iii is reached, when respiratory depression begins.

Pupils. The usual changes in pupillary size occurring in the different planes of surgical anesthesia may be seen in Figure 3. When morphine and atropine (or scopolamine) are employed, the action of morphine on the iris usually predominates. Thus the pupil is somewhat constricted in comparison with the usual state for a given plane of anesthesia.

Normally the pupils are constricted as in natural sleep during stage III, especially in plane ii, and react only sluggishly to strong light. Reflex dilatation



STAGES OF ANESTHESIA		RESPIRATION Thoracic	RESPIRATION Abdominal	PUPIL SIZE without preliminary medication	EYEBALL ACTIVITY	REFLEXES Corneal	REFLEXES Conjunctival	REFLEXES Pharyngeal	REFLEXES Cutaneous	REFLEXES Peritoneal	PULSE	BLOOD PRESSURE	EXAMPLES OF OPERATIVE PROCEDURES
I ANALGESIA					Voluntary	+	+	+	+	+	Fast	Elevated	First Stage of Labor
II DELIRIUM					++++	+	+	+	+	+	Fast	Elevated	None
III SURGICAL	Plane i				++++ +++ ++ +	+	–	+	+	+	Normal	Normal	Thoracic Surgery Laminectomy
									–				Cesarean Thyroid Brain Mastoid Bladder Urethra Fractures Eye Nose Head and Neck Obstetrical Delivery Hernia
	Plane ii				Fixed	+	–	–	–	+	Normal	Normal	Tonsils Joints Larynx Rectum
						–				–			Most Abdominal Surgery
	Plane iii				Fixed and Converged	–	–	–	–	–	Fast	Falling	Some Abdominal Surgery Internal Podalic Version Breech Extraction
	Plane iv					–	–	–	–	–	Fast and Feeble	Falling	
IV MEDULLARY PARALYSIS						–	–	–	–	–	Absent	Shock Level	

FIGURE 3. *Stages of anesthesia.*

Schematic representation of changes in important physical signs at various levels of anesthesia, and the correlation of depths of anesthesia with the control of surgical reflexes and with specific surgical procedures. See text for details.

characteristic of stage II does not occur. The pupillary constriction of stage III is ascribed to abolition of cerebral impulses which inhibit the tone of the oculomotor constrictor center (Edinger-Westphal nucleus).

The pupils dilate progressively as plane iv is approached, and this dilatation is paralytic rather than reflex in character. Pupillary dilatation is greatest with those anesthetics causing the most marked loss of muscle tone, the tone of the sphincter muscle of the iris reflecting, in the deeper planes of anesthesia, the tone of other smooth muscles of the body. Both the direct action of the anesthetic agent and the accompanying anoxia account for the paralytic dilatation. Relatively impotent anesthetics such as ethylene and nitrous oxide, when given with adequate oxygen, do not cause paralysis of the iris. In the stage of medullary paralysis, the pupils dilate widely and rather rapidly. Sometimes sudden dilatation of the pupils is confusing because it may represent either the dangerous advent of plane iv, which requires immediate withdrawal of the anesthetic, or a re-entrance into the second stage, which requires an increase in concentration of anesthetic vapor. The question can be settled quickly by looking for eye movements, testing the corneal and other reflexes, and observing the character of the respiration. Fixed eyeballs and the absence of corneal reflexes always accompany pupillary dilatation arising from dangerously deep anesthesia, and lacrimal secretion has always stopped. When one is in doubt, the anesthesia should be temporarily discontinued.

Eyeball Movements. Activity of the eyeball is an important aid in recognizing quickly the stage and plane of anesthesia. The factors which control ocular activity during anesthesia are unknown. The changes in movements of the eyeball in the various stages are shown in Figure 3, and their significance has been pointed out. The "roving eyeball" is one that rhythmically oscillates, nearly always in a lateral direction, because of alternate contraction of opposite muscles. Often, however, the eyeballs may be eccentric and stationary for several seconds or even minutes, and then move to the corresponding position on the opposite side. If the oscillation is entirely across the palpebral slit, or if the eccentric fixation is extremely to one side, the patient is in the upper border of plane i. These extremes of eyeball movement decrease until they are minimal, at which time the patient is in the lower border of plane i. Plane ii has been reached when all ocular movements cease. The exact type of motor activity of the eyeball is unimportant, although a given individual usually manifests the same type throughout anesthesia. However, the degree of activity serves as a guide to the depth of anesthesia.

Sensory Reflexes. The progressive loss of cutaneous, mucosal and other sensory reflexes as anesthesia deepens may be studied in Figure 3. It is obvious that most abdominal operations cannot be performed easily until plane ii is reached because not until then are the peritoneal reflexes abolished or is muscular relaxation sufficiently complete to render the abdominal wall flaccid. The corneal, genital and peritoneal reflexes are the last to disappear, at which time motor reflex centers in the cord are completely paralyzed.

Peripheral Nervous System. Even during surgical anesthesia, direct excitation of skeletal muscles and peripheral somatic nerves results in the usual responses. While it is true that volatile anesthetic vapors, applied directly to nerves, act as local anesthetics and abolish excitability and conductivity first of sensory and then of motor nerves, this effect requires higher concentrations than can be obtained in living animals by systemic administration.

Blood Pressure and Pulse Rate. These cardiovascular indices are practically normal during planes i and ii. The pulse is usually full. In plane iii both the cardiac rate and blood pressure may be temporarily elevated, but the latter soon falls if anesthesia is sustained in this plane. In plane iv, the blood pressure drops precipitously and the pulse, after an interval of compensatory acceleration, becomes feeble and finally cannot be obtained. Respirations cease before the heart stops beating.

Temperature. Body temperature falls progressively during the course of surgical operations. This is due to lessened muscular activity, increased heat loss from dilated peripheral vessels incident to mild vasomotor depression, the cooling effect of the anesthetic vapors and to interference with the regulation of body temperature by the central nervous system. Thus the patient receiving anesthesia is warmly clothed and blanketed, and operating rooms likewise are kept quite warm. The average fall in rectal temperature during the first hour of ether anesthesia is about two degrees F.

Fourth Stage: Medullary Paralysis. This stage follows plane iv of stage III and ends with death. It starts as soon as the weakened respiration of plane iv entirely ceases, and is characterized by medullary paralysis, respiratory arrest and vasomotor collapse. If there is any indication that the patient is reaching plane iv all other procedures immediately become quite secondary to the necessity for lightening the anesthesia by withdrawing the anesthetic vapor and administering air or oxygen.

The paralytic stage is preceded by several important warning signals. (1) Abdominal respiration signifies the paralysis of intercostal muscles and the presence of plane iii. (2) The pupils start dilating in lower plane ii when the usual preanesthetic medication with morphine and atropine or scopolamine has been employed. The dilatation progresses as plane iii advances, and is almost complete in plane iv. The eyes are dry and lusterless. (3) The pulse quickens in plane iii and continues to accelerate as anesthesia deepens. This is a compensatory response to the respiratory and vasomotor depression. (4) Cyanosis secondary to respiratory and circulatory changes develops as the paralytic stage is approached. It is not a dependable sign, however, when cyclopropane is used.

The *signs of approaching death* in the stage of medullary paralysis from anesthesia are well-known but may be summarized at this juncture. All the superficial and deep reflexes are absent, and the sphincter muscles relax so that the rectum and bladder may empty. The skin is cold and gray, and often the clammy cold sweat of terminal "agony" appears. The pupils are widely dilated and paralyzed, and the eyes fixed and staring. The pulse is either feeble and slow, or more often unobtainable. The blood pressure is at a shock level or unreadable. The abdominal respiration of plane iii becomes shallow and irregular, then labored and gasping, and finally stops.

Respiration ceases before the heart stops beating. This is important because, upon withdrawal of anesthesia and the application of artificial respiration and resuscitative measures, the still active circulation allows excretion of the anesthetic to occur through the lungs, thereby lowering the concentration of anesthetic in the brain. After a few deep artificial respirations, sufficient blood will have passed through the lungs to allow the removal of enough anesthetic to revive the medulla and return the patient to stage III. This obviously would not be possible if cardiac arrest occurred before respiratory failure, under which circumstances artificial respiration would be of no avail.

In this regard, there is a fundamental and important difference between chloroform and other anesthetics. While with most anesthetics respiration ceases first, by the time respiration fails from chloroform, the cardiovascular system is depressed to the point of functional inadequacy. Although the heart still beats, the blood pressure is so low and cardiac systole so feeble that, despite the administration of artificial respiration, circulation through the lungs is insufficient to rid the body of the toxic concentration of the drug.

The *time of death* after cessation of respiration depends on the ratio of metabolic rate to the oxygen reserve. It may be four or five minutes if the metabolic rate is low and the oxygen reserve high, or it may be one or two minutes if the reverse is true. When respiratory arrest occurs during anesthesia, artificial respiration should be started *at once,* regardless of the cause.

Recovery from Anesthesia. The speed of recovery from surgical anesthesia is dependent on the agent used rather than on the duration of anesthesia. The recovery period is relatively long after avertin, ether and chloroform and very short after ethylene, cyclopropane and divinyl ether. After the use of ether and chloroform, the return to full consciousness requires from one-half hour to two hours or longer, and this is then followed by a long postanesthetic sleep. Hyperpnea hastens the emergence from anesthesia produced by volatile agents and this can be induced by carbon dioxide. After ethylene, divinyl ether and cyclopropane, consciousness returns in a few minutes.

Soon after the removal of the anesthetic mask, the respirations become more quiet. The reflexes return in the reverse order of their disappearance. Swallowing movements appear and vomiting may occur, especially if ether was employed. The patient may go through a short period of excitement before awakening. This emergence excitement is usually rather mild as compared with induction delirium, perhaps because aggravating stimuli such as noises, pain, and apprehension are now absent. Furthermore, post-surgical depression limits physical activity. Postanesthetic sleep often follows the return to consciousness and may last many hours. The character of the recovery period following the various anesthetics frequently determines the surgeon's choice of agent. Particularly desirable features are lack of vomiting and early return of cough reflexes. Postanesthetic sleep may or may not be advantageous.

Depth of Anesthesia in Relation to Control of Surgical Reflexes. Knowledge of the order in which the reflexes disappear during the various stages of anesthesia enables one to have the patient in the proper plane for the surgical procedure to be performed, and thus the dangers of too light or too deep anesthesia can be avoided. The time of disappearance of the major surgical reflexes is indicated in Figure 3, but certain additional points deserve mention. Special texts on anesthesia and surgery should be consulted for further details (*see* especially Guedel, 1937; Beecher, 1938).

The *viscera* give rise to little or no pain during operations; thus surgery of the gastrointestinal tract, liver, spleen, pancreas, omentum, kidney, etc., can be performed in the upper half of the first plane of stage III. Traction on the fibrous attachments of these structures, however, causes pain and requires deeper anesthesia. The reflex responses to surgical trauma of the *brain* and *bones* also are annulled in upper plane i anesthesia. The same is true of the skin, but mucocutaneous junctions are very sensitive. Anal or vaginal surgery, therefore, requires deeper anesthesia. In regard to the mucosa of the *posterior pharynx,* more than pain sense is involved because reflex swallowing, stimulated by local manipulation, may be followed by retching and aspiration of débris. This danger is past when lower plane i is reached because the posterior pharyngeal reflex is then inactive. The *laryngeal reflex* is more persistent and necessitates for its abolition anesthesia in upper plane ii. For example, it is impossible to insert an endotracheal catheter under light anesthesia without exciting a prolonged spasm of coughing.

Traction or resection of *nerve trunks* without causing reflex movement or respiratory stimulation (often resulting in vocal cord adduction) can usually be performed in lower plane i. Reflexes arising from *skeletal muscles* are rather complicated. Local reflexes are of no importance but generalized responses depend on the size of the muscle and the type of stimulation. The muscles of the abdominal wall may be rendered sufficiently flaccid for surgery by lower plane ii anesthesia. In contrast, very deep anesthesia is required to abolish the reflexes of the anal sphincter. These are sometimes still active in plane iv. On rare occasion, advantage of this fact is taken by divulsing the anal sphincter in order to stimulate respiration when the latter has ceased.

Traction reflexes are particularly troublesome and require the constant attention of the anesthetist. They arise from pulling on the mesentery or the fibrous attachments of the viscera of the abdomen and pelvis, and manifest themselves in a contraction of the abdominal wall which may push the intestines out through the incision, in respiratory acceleration and in adduction of the vocal cords. A similar spasm of the vocal cords is elicitable experimentally by electrical stimulation of the splanchnic nerves. The respiratory effects may still be present in plane iii, but the response of the abdominal wall is prevented in lower plane ii. When traction on viscera is to be made, the anesthetist must anticipate this maneuver by deepening the anesthesia. A traction reflex still more difficult to combat is the *subdiaphragmatic reflex*. This is present especially in upper abdominal surgery, but in the presence of peritonitis it may be elicited by any intraperitoneal procedure. It manifests itself in an adduction of the vocal cords which causes a characteristic crowing inspiration and grunting expiration. The contraction of the muscles of the abdomen to force expiration against the closed glottis is particularly annoying. Third plane anesthesia sometimes abolishes this reflex but entails troublesome diaphragmatic respiration. An endotracheal airway is the best means of circumventing closure of the glottis, and this holds true for spastic adduction of the vocal cords regardless of the cause.

Smooth muscle tone is affected more by the direct action of the anesthetic agent on the muscle than by reflexes of the nervous system. The musculature of the intestinal tract is greatly depressed in plane iii, and peristalsis stops. At this depth of anesthesia there is also loss of tone of the smooth muscle of blood vessels. These factors, combined with the skeletal muscle flaccidity of plane iii, account for the loss of peripheral circulatory support and the resulting anesthetic shock. It is estimated that anesthesia for one-quarter hour in plane iii causes greater depression of the circulation than anesthesia for two hours in plane i.

Depth of Anesthesia in Relation to Specific Surgical Procedures. Some of the more common surgical procedures and the planes in which they may be performed are indicated in Figure 3. Certain additional points may be emphasized.

During the lower half of stage I, analgesia is present, but no painful procedures are permissible. Consciousness is clouded, and when pain is superimposed on disturbed consciousness delirium may result. The phenomenon is also seen when hypnotics are given to induce sleep in patients who have pain. In order to prevent or control delirium due to pain, morphine should be given or sufficient anesthetic should be administered to carry the depth of anesthesia to plane i of stage III.

Obstetrical analgesia in the first stage of labor is essentially an attempt to make use of stage I anesthesia to relieve pain and yet retain sufficient consciousness to allow the patient to cooperate. The difficulties of obtaining satisfactory obstetrical analgesia are only too well known. Morphine is not permissible in doses capable of alleviating labor pains, and attempts to secure amnesia with scopolamine or barbiturates frequently cause delirium. The use of specific anesthetics in labor will be discussed later.

The first and second planes of stage III anesthesia are suitable for the performance of nearly all surgical operations. Most abdominal surgery is possible in the lower half of plane ii which usually affords maximal muscular relaxation. As a rule, this depth is needed only until the visceral structures are explored, elevated, and the field packed off, and during peritoneal closures. Maximal relaxation of abdominal muscles, however, may not always be obtained before intercostal paralysis has started. This means that the annoyance of increased diaphragmatic movement must be endured if abdominal relaxation is important.

Surgery of the head and neck is usually performed with lower plane i anesthesia in order to prevent vomiting which would prove troublesome. Whenever endotracheal anesthesia is used for any operation, regardless of its nature, upper plane ii anesthesia must be maintained in order to avoid the coughing spasm which the catheter would otherwise induce. First plane anesthesia is essential in all chest surgery in which it is imperative that an active cough reflex be maintained. Tonsillectomy is performed in the lower plane i by those who place emphasis on the retention of the cough reflex. The tongue does not relax until this depth is reached and therefore tonsillectomy cannot be performed with lighter anesthesia. Most surgeons desire upper plane ii anesthesia for tonsillectomy because this allows a well relaxed throat, although the danger of aspiration of blood and débris is enhanced.

In obstetrics, lower plane i affords sufficient anesthesia for normal deliveries and low forceps extractions. The anesthetist must choose between a relaxed perineum and retention of full activity of the uterine musculature. Insufficient perineal relaxation may result in extensive lacerations. Lower plane i anesthesia is safest for most obstetrical surgery.

Third plane anesthesia has few uses in surgery. Its main employment is in obstetrics for internal podalic version and extraction, and for breech delivery.

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Haggard, H. W. The absorption, distribution, and elimination of ethyl ether. III. The relation of the concentration of ether, or any similar volatile substance, in the central nervous system to the concentration in the arterial blood, and the buffer action of the body. *J. Biol. Chem.*, 1924, **59**, 771–781.

CHAPTER 4

PREANESTHETIC MEDICATION, TECHNIC OF ANESTHESIA AND ANESTHETIC ACCIDENTS

PREANESTHETIC MEDICATION

Preanesthetic medication refers to the use of one or more drugs prior to the administration of an anesthetic for the purpose of making anesthesia safer and more agreeable for the patient. Such medication is nearly always a routine procedure before general anesthesia.

The more specific objects of this medication are to lessen apprehension and quiet the patient, to reduce the amount of anesthetic needed and in this manner to lessen its toxicity, and to counteract certain untoward or undesirable effects such as the respiratory irregularities of the excitement stage and the excessive flow of mucus or saliva. By decreasing the patient's reflex excitability, proper preanesthetic medication also permits the use of certain inhalation anesthetics (ethylene, nitrous oxide) which otherwise could not possibly produce complete surgical anesthesia without asphyxia. In other words, all preanesthetic medication routines are designed to make the anesthesia more safe and comfortable for the patient and more efficient for the surgeon. It should never be forgotten that the patient comes to the operating room not for an anesthetic but for an operation, and the former serves only to enhance the chances for the success of the latter.

As a rule, most preanesthetic medication consists of a combination of a sedative or narcotic drug with one that will diminish secretions of the respiratory tract and inhibit salivation. The narcotic most commonly used is morphine, but sedatives such as barbiturates are also employed. The agent given to lessen secretions is atropine or scopolamine. The latter drug, in addition, has certain depressant actions on the central nervous system. These medicaments may be discussed individually in regard to their preanesthetic use and value.

Morphine. Since morphine was first used clinically for preanesthetic medication by Labbé and Guyon in 1872, it has occupied the major position in all drug combinations for this purpose. Morphine sulfate in the average adult dose of 10 to 15 mgm is usually injected hypodermically one to one and one-half hours before induction of anesthesia. Some anesthetists prefer to divide the morphine into two equal doses, given respectively two hours and one hour before anesthesia. The time interval between the injection of morphine and the induction of surgical anesthesia should be sufficiently long so that the peak of the respiratory depressant action of the alkaloid has already been passed. It is impossible to depend on a fixed dose of morphine because the character of the response varies with the patient's condition. This is clearly seen in persons with hypothyroidism who are very susceptible to morphine and in whom five mgm may cause profound depression for many hours. In contrast, a patient with hyperthyroidism may receive 15 mgm and note little effect.

Morphine has definite *advantages* as a preanesthetic agent. It relieves pain, decreases anxiety and hence lessens the struggle, excitement and delirium of the induction period. In this way, the onset of anesthesia is made smoother and more rapid. By lessening reflex excitability, morphine decreases the amount of anesthetic needed for surgical anesthesia. This widens the margin of safety and lessens the likelihood of pulmonary and other complications. The respiratory reflexes are sufficiently obtunded so that the respiratory irregularities which are a constant source of trouble and danger in the induction period are mitigated. Morphine narcosis sometimes extends into the postoperative period and aids in relieving pain and promoting rest.

On the other hand, morphine has definite *disadvantages*. The drug is constipating, an action which undoubtedly plays a significant rôle in the high incidence of postoperative ileus. Morphine interferes with the value of pupillary size as a physical sign of the stages of anesthesia. Morphine miosis usually takes slight precedence over atropine mydriasis when the two drugs are used together in the usual doses. The respiratory depression caused by morphine may coincide with that of deep surgical anesthesia. Also, the depression of respiration by morphine, if exaggerated for any reason, may make difficult the induction of inhalation anesthesia because of the lessened respiratory minute volume. This difficulty may be particularly marked with open ether administration, in which instance the concentration of ether must be elevated to induce anesthesia. Spasm of the glottis may then result because the irritability of the larynx is not commensurately reduced by morphine. Rather than increase the concentration of the anesthetic, carbon dioxide should be administered, a simple procedure when a closed system is employed. The mechanism of respiratory arrest during the induction period, due to overzealous medication with morphine, has been discussed on page 37.

Atropine. Atropine is probably second in importance as an agent for preanesthetic medication, despite the increasing use of scopolamine in recent years. Atropine sulfate is usually given hypodermically in the dose of 0.3 to 0.5 mgm. The main purpose of the drug is to prevent excessive secretions of the respiratory tract and salivary glands, but it also acts as a mild respiratory stimulant. Atropine need not be used with anesthetics such as ethylene and nitrous oxide which do not cause mucus or salivary secretion.

Atropine has certain distinct *advantages*. The inhibition of secretions definitely lessens the incidence of postoperative pulmonary complications and vomiting, and allows the use of certain inhalation agents which would otherwise be contraindicated. Atropine in ordinary doses is a mild respiratory stimulant and may aid in offsetting undue depression of respiration by morphine or the anesthetic. It has been claimed that atropine lessens the possibility of cardiac arrhythmias or arrest during the induction of anesthesia, especially when chloroform is used. The usual explanation given is that reflex vagal activity is inhibited. The facts, however, do not support this contention. In the first place, the dose of atropine is insufficient to block the peripheral action of the vagus on the heart; indeed, it may tend slightly to stimulate the vagus center. Secondly, arrhythmias produced by chloroform and certain other vapors are not due to vagal impulses. The nerve impulses which may assist in causing these cardiac effects are mediated through the sympathetic pathways.

The *disadvantage* of atropine is that it interferes with pupillary signs. The anesthetist, however, has more dependable indices of the depth of anesthesia.

Scopolamine. Many anesthetists and surgeons have substituted scopolamine and morphine for atropine and morphine. Scopolamine, like atropine, has a potent inhibitory action on secretions but in addition the alkaloid is also a depressant of the central nervous system and reduces excitement. It is claimed that scopolamine has exceptional tranquilizing properties. Certainly it is effective in relieving the patient's emotional disturbances. The drug also produces amnesia. In the presence of pain, scopolamine is likely to cause delirium and should not be given unless morphine is also used. Scopolamine hydrobromide is injected subcutaneously in the adult dose of 0.3 to 0.6 mgm.

The *advantages* of scopolamine are its tranquilizing action, its ability to inhibit secretions, and its facilitation, when properly balanced with morphine, of the induction of anesthesia. Careful studies on man by Waters and associates (1938) indicate that scopolamine apparently does not increase the medullary depressant effects of morphine but rather antagonizes them. This finding is important because it is usually stated that scopolamine is additive to morphine in this regard.

The *disadvantages* of scopolamine are considered negligible by those who have had wide experience with the drug. It is usually taught that scopolamine differs from atropine in being a respiratory depressant but studies on man do not support this contention. In fact, the alkaloid may exert a stimulating action on respiration. In the experiments of Waters and coworkers to which reference has been made, a total of 128 mgm (!) of morphine was given with 4.2 mgm of scopolamine in six divided doses over a period of two and one-half hours. Sufficient muscular relaxation and anesthesia were obtained with these two drugs alone to enable the repair of a large ventral hernia. This procedure is not advised, but the point of interest is that adequate pulmonary ventilation was maintained. It is evident that scopolamine must have protected against the respiratory depression caused by the exceptionally large amount of morphine. Like atropine, scopolamine interferes with pupillary signs. It should not be used alone for preanesthetic medication in the presence of pain. The main disadvantage of scopolamine is that idiosyncrasy to it is fairly common and the patient may manifest excitement or delirium (page 463).

Barbiturates. The use of barbiturates for and prior to anesthesia is also discussed in Chapter 9. Their employment is ordinarily reserved for producing sound sleep the night before operation. In other instances, the barbiturates are used for basal or obstetrical anesthesia. Occasionally, the ultra short-acting members are used intravenously as general anesthetics for minor surgical procedures. The barbiturates are rarely substituted for morphine because they are not analgesic. Given alone, they do not affect the pupillary responses during anesthesia.

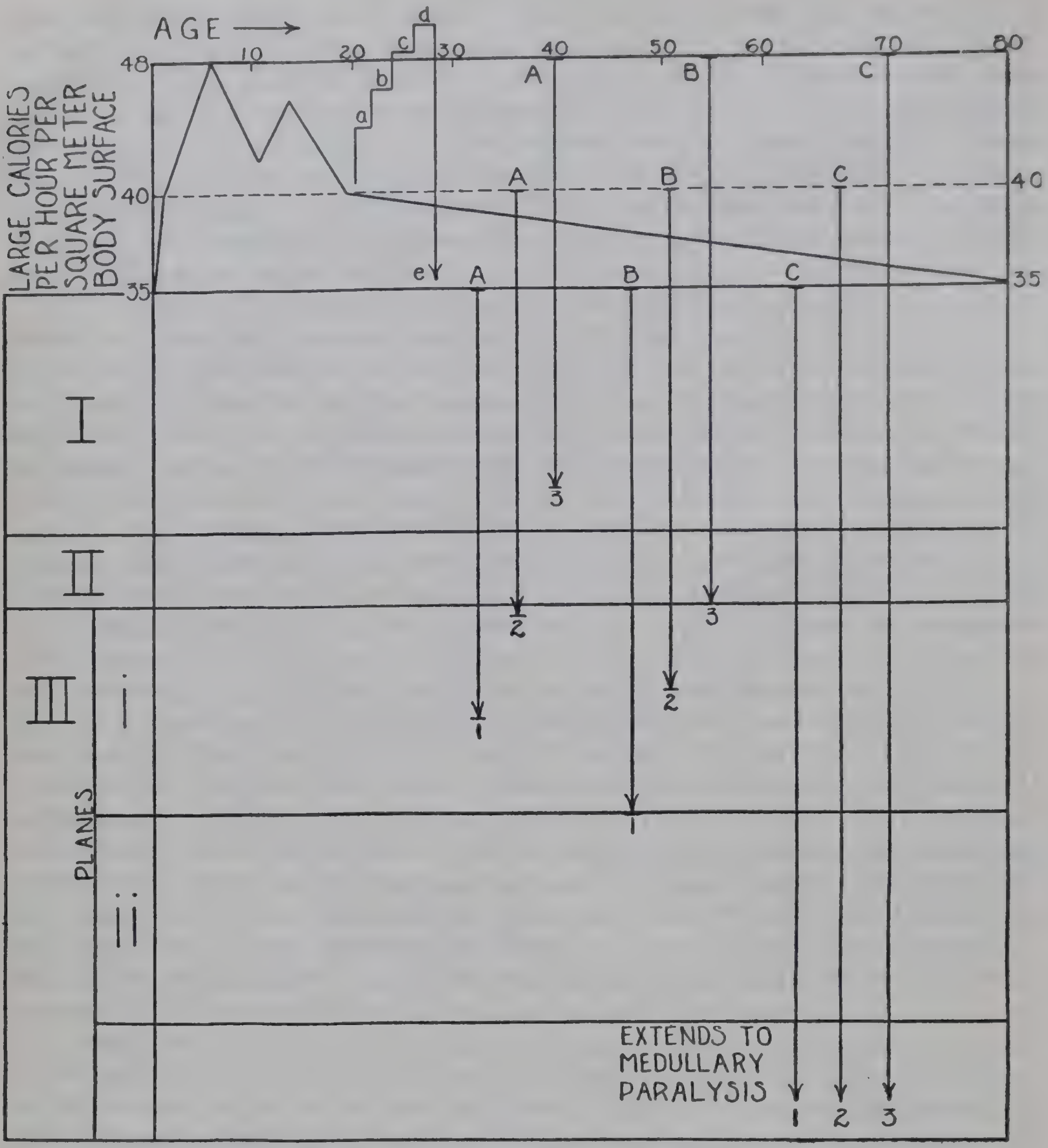
Tribromethanol. Tribromethanol is used primarily for basal anesthesia, so that the patient is unconscious when he reaches the operating room. Avertin is fully discussed in Chapter 7.

Factors Modifying Preanesthetic Medication. The amount of anesthetic necessary to obtain a given degree of anesthesia varies especially with the reflex excitability of the nervous system. The higher the level of the reflex excitability, the greater is the resistance to anesthesia. More anesthetic is then required and the attendant danger is increased. To diminish the reflex excitability and thus increase the margin of safety of the anesthetic agent is one of the main purposes of preanesthetic medication. At certain levels of nervous system excitability, it is impossible, without preliminary medication, to anesthetize a patient with ethylene or nitrous oxide without the occurrence of marked asphyxia. In this connection, a second important factor merits consideration, that is, the oxygen needs of the patient. When the total metabolism is high, due to conditions associated with the patient's disease, more oxygen is required and consequently less room is available in the anesthetic mixture for ethylene or nitrous oxide, and anesthesia may be unsatisfactory or impossible. Under many circumstances, nervous system excitability and oxygen demands tend to rise and fall together. The anesthetist has therefore come to view these two factors as associated with each other in determining the necessity for preanesthetic medication.

The height of reflex excitability of the nervous system is the level from which anesthesia starts. The practical application of this fact is graphically illustrated in Figure 4 (Guedel, 1937). This figure presents the normal basal metabolic rate at different ages as compared with the base line value at birth and extreme old age of 35 large calories per hour per square meter of body surface. The curve depicting basal metabolic rate also serves to show the reflex irritability of the nervous system, and agents used to produce preanesthetic sedation tend to lower both excessively elevated oxygen demands and reflex excitability. In the chart is likewise shown the effect of specific conditions which tend to increase oxygen demand and reflex irritability, and thus elevate further the starting point for the induction of anesthesia. These specific conditions now merit brief consideration.

Specific Factors Modifying Reflex Irritability and Oxygen Demand. The factors which tend to influence reflex excitability and oxygen demand are (1) age, (2) pain, (3) fever, (4) thyroid disease, (5) body build, (6) toxemia, and (7) emotional disturbances. Often several of these factors operate together and mutually influence each other. The influence of *age* on oxygen requirements and reflex excitability may be seen in Figure 4. *Pain* increases the irritability of the nervous system and raises the resistance to anesthesia. Its effects vary in different individuals and are more pronounced, for example, in a hyperthyroid than in a hypothyroid patient. *Elevation of the temperature* of only one degree F. is accompanied by an increase of more than seven per cent in the metabolic rate, and the reflex excitability of the nervous system is correspondingly increased. Emotional disturbances and sensitivity to pain are greater in the presence of fever. *Endocrine dysfunction,* especially of the thyroid gland, notably affects oxygen needs and nervous irritability. Patients with a very muscular *body build* are more difficult to anesthetize than slender asthenic individuals. Certain *toxic states* render the nervous system more excitable. The *emotion* of fear is one of the most important factors in raising reflex excitability. In Figure 4 is presented an example of the influence of several of the factors mentioned in a hypothetical case of hyperthyroidism. The increments over the normal reflex excitability and oxygen requirement due to the disease itself, fear, fever and pain are illustrated, as well as the effect of preanesthetic medication.

The Influence of Preanesthetic Medication on the Depth of Anesthesia. When the weaker anesthetic gases are employed in patients with elevated reflex excitability, an adequate depth of anesthesia may not be obtainable without proper preanesthetic medication. In contrast, when more potent anesthetics such as ether and cyclopropane are employed, any desired depth of anesthesia may be obtained without preanesthetic medication and regardless of the initial level of reflex excitability. However, when reflex excitability is elevated, a proportionately greater blood concentration of anesthetic agent is necessary for a given plane of anesthesia. Under these circumstances, preanesthetic medication decreases the amount of anesthetic required and thus widens the margin of safety.


AGE
10
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80
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40
35
LARGE CALORIES PER HOUR PER SQUARE METER BODY SURFACE
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b
c
d
e
A
B
C
A
B
C
A
B
C
I
II
III
i
ii
PLANES
3
2
3
1
2
1
EXTENDS TO MEDULLARY PARALYSIS
1
2
3

FIGURE 4. *Schematic representation of the planes of anesthesia obtainable when using various anesthetic agents with and without preanesthetic medication.*

Superimposed on the diagram of the planes of anesthesia is a schematization of the reflex excitability of the nervous system at different ages as depicted by basal oxygen demands (see text). *A, nitrous oxide; B, ethylene; C, ether, divinyl ether* or *cyclopropane.* The vertical lines *A–1, A–2* and *A–3* represent the depths of anesthesia obtainable with nitrous oxide when anesthesia is started at three levels of reflex excitability and oxygen demand. Even under the most favorable circumstances (*A–1*), anesthesia cannot be carried with an 88:12 nitrous oxide-oxygen mixture more than 15 per cent through stage III, *i.e.,* a little below mid-plane i, and therefore nitrous oxide has been given a potency rating of 15 per cent. With ethylene and sufficient oxygen to prevent anoxia, under favorable circumstances (*B–1*) anesthesia can be carried to the upper border of plane ii, *i.e.,* 25 per cent through stage III, and therefore this gas has been given a potency rating of 25 per cent. If anesthesia with nitrous oxide or ethylene begins from higher levels of reflex excitability, these gases are even less effective (*A–2, B–2*). If the starting point is sufficiently high, anesthesia may be impossible (*A–3, B–3*) without the intervention of anoxia or preanesthetic sedation. Regardless of the initial level of reflex excitability, ether, divinyl ether and cyclopropane, unassisted by anoxia or preliminary medication, can carry anesthesia to medullary paralysis (*C–1, C–2, C–3*) and therefore have a potency rating of 100 per cent.

The figures *a, b, c* and *d* indicate increments of added reflex excitability and excess oxygen

Additional Preanesthetic Preparation of the Patient. Only the more important points to be observed in the preanesthetic preparation of the patient can be mentioned here (for details, *see* Symposium, 1940). The diet should be light during the day prior to operation, and it is desirable to increase carbohydrates and proteins and to restrict fats in order to protect the liver (page 66). If the operation is an emergency and the patient has recently ingested food, the gastric tube should be passed and the stomach emptied to lessen the danger of aspiration or asphyxia should vomiting occur. The former routine of purging is obsolete.

Special attention should be given to the cardiac, pulmonary, renal and hepatic functions during the usual physical and laboratory examinations of the patient. The results of these often determine the choice of the anesthetic agent. A poor choice greatly increases the surgical risk and may result in death.

The patient should be kept sufficiently warm during the operation to minimize the loss of body heat occurring during anesthesia. The eyes should be closed and protected from anesthetic vapors. The corneal reflex is not used as a physical sign because of the danger of inflicting damage. The nose and lips may be prepared with vaseline, and the airway is carefully examined to make certain that no potential obstruction such as false teeth or removable bridgework is present.

POSTANESTHETIC MANAGEMENT

Postoperative care is chiefly a surgical question but certain points may be mentioned here concerning the postanesthetic management. (For details, *see* Symposium, 1940.) Skillful nursing is the main requirement. The patient must be watched continuously until conscious. If vomiting occurs, care should be taken to prevent aspiration. With some agents, vomiting during the recovery phase is so frequent that it has come to be looked upon as an attendant phenomenon rather than as an accident. The tongue should be prevented, by a mechanical airway, from falling back into the throat and asphyxiating the patient.

On some surgical services, the periodic inhalation of carbon dioxide (five or 10 per cent) is routinely used to cause hyperpnea and clear the bronchial tree. The purpose of this is to prevent atelectasis and reduce the incidence of postanesthetic pneumonia. The statistical evidence for the value of this procedure is inconclusive. The inhalation of carbon dioxide is also helpful to arrest persistent postoperative hiccoughing.

Attention should be paid to the recovery of bladder and intestinal functions. Postanesthetic urinary retention and intestinal ileus are frequent and troublesome. In addition to numerous mechanical measures for obtaining relief and hastening recovery, certain drugs such as choline esters, posterior pituitary and prostigmine are available.

The postoperative relief of pain is a problem which depends largely on the type of surgical procedure performed. In general, relief with opiates may be allowed for twenty-four hours, but after the first postoperative day analgesic medication should not be given in amounts or at intervals which will interfere with the proper interpretation of the surgical results or mask the onset of complications.

TECHNIC OF ANESTHESIA

The many methods and instruments used in the administration of the various anesthetic agents cannot be fully described here. The problems are technical and are best learned by actual training on an anesthesia service. Certain general features, however, must be pointed out. Ethylene, cyclopropane and nitrous oxide

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demand in a hypothetical case of hyperthyroidism in a 20 year old youth. The increment due to *hyperthyroidism* is represented by *a; pain, b; fever, c; emotional disturbance, d.* The vertical line *d–e* represents the effect of intelligent preanesthetic sedation on reflex excitability. Thus surgical anesthesia with the weaker anesthetic gases is made possible and higher concentrations of oxygen may be used. If the more potent agents are used, a given level of anesthesia can be obtained with a lower concentration of anesthetic. (After Guedel, 1937.)

require special gas machines for their use. They cannot be given except through a closed system with oxygen or air. Ether, divinyl ether, ethyl chloride and chloroform can be given either by the *open, semi-open,* or *closed* technics. Tribromethanol, on the other hand, is given rectally.

Open Method. Ether may be used to illustrate the open method of administering an anesthetic because the open drop ether technic is still the most common type of anesthesia used in the United States. The open method consists in dropping the anesthetic on a multi-layered gauze mask with free access of air, and no attempt is made to confine the vapor.

The rate at which the ether is dropped varies with the size of the drop and the thickness of the mask; it is usually 12 drops during the first minute, 24 during the second, 48 during the third and 96 during the fourth. By this time the ordinary mask is saturated and the concentration of ether under the mask has approached 10 volumes per cent. Also, by this time, the patient is in the second or excitement stage of anesthesia. The rate of approximately 100 drops per minute is continued for about 15 minutes. During this interval, the concentration of ether under the mask is much higher than is later needed to maintain the desired depth of anesthesia. The reason for this procedure is that the brain attains a given saturation with ether in a shorter period than do the other tissues which then act as a huge buffer system withdrawing anesthetic from the brain until all the tissues obtain their quota. In the ordinary anesthetization of an adult one must therefore keep the mask completely saturated for approximately 10 to 15 minutes. The rate of administration of ether is then slowly decreased so that the average rate during the second 15 minutes of anesthesia is approximately 50 drops per minute. During this time equilibrium is being reached, a process probably requiring between 30 and 45 minutes. The rate during the third 15 minutes is approximately 20 to 30 drops per minute. For the fourth 15 minute interval and the subsequent period of anesthesia, the rate of administration is kept at a maintenance level of approximately 12 to 24 drops per minute. The concentration of ether in the mask during this maintenance period is between three and five volumes per cent. The foregoing description is not quantitative and serves only as a guide. The open drop method is wasteful and only a small fraction of the ether used actually enters the body. During an hour's anesthesia, three-quarters to one pound of ether may be used in contrast to the two ounces needed when the closed carbon dioxide absorption technic is employed.

Chloroform anesthesia by the open method requires the same technic described for ether. Chloroform, however, is much more potent and less volatile than ether. For every six drops of ether placed on the mask, one drop of chloroform may be considered as the approximate equivalent.

Semi-open Method. This technic is also called the semi-closed method. A gauze mask is used as in the open method but a towel is so placed on the face and around the base of the mask that the escape of anesthetic vapors is greatly decreased and more carbon dioxide is retained. The rebreathing of this carbon dioxide prevents the apnea which may occur during induction by the open method (page 37), and facilitates the rapid onset of anesthesia.

The anesthetist has several means for controlling the administration of anesthetic vapor by the open or semi-open mask method. Not only can he regulate the rate at which ether is dropped on the mask, but the distance at which the mask is held from the face and the amount of air accessible to the patient can be changed. Fine control is especially important during the induction phase.

Closed Method. With this method, the patient rebreathes the anesthetic mixture. The usual apparatus consists of a tight fitting mask, rebreathing bag, and provisions for the absorption of moisture and carbon dioxide and for the introduction of anesthetics, oxygen and carbon dioxide. In the strict sense, this is the only type of system which can be considered "closed." Anesthesia by the closed method has many advantages, chief among which are the adequate control of respiration which it allows, economy in the cost of anesthesia, preservation of body heat and water, smoother induction, and moment to moment control of depth of anesthesia.

When nitrous oxide, ethylene, or cyclopropane is used with oxygen and the closed method, there is liberation of nitrogen from the body fluids through the lungs. This nitrogen represents that which was held in simple solution in the blood as a result of its presence to the extent of 80 per cent in the inhaled air. The anesthetic mixture contains no nitrogen and consequently the partial pressure of nitrogen in the alveoli of the lungs is greatly reduced, causing an escape of nitrogen from the body fluids and its accumulation in the breathing bag (Guedel, 1937). Three liters of this gas may be liberated through the lungs during the first hour of anesthesia, and in a closed system will greatly dilute the anesthetic mixture. Unless the breathing bag is emptied periodically to dispose of the accumulating nitrogen, the anesthetic mixture will become too weak to maintain surgical anesthesia, or the dilution will be made at the expense of the available oxygen which is already minimal for body needs when ethylene or nitrous oxide is employed.

It should be emphasized that the development of instruments and machines to facilitate the administration of anesthesia does not lessen the necessity for close observation of the patient. Nothing can replace the alert and intelligent attentiveness of a trained anesthetist. No rigid routine can be adopted with safety, and the vital signs must be continuously watched from moment to moment so that any untoward change may be properly and immediately countered. A gas machine can assist but not replace an anesthetist.

ANESTHETIC ACCIDENTS

A number of accidents may occur incident to the administration of an anesthetic. It is important to anticipate and prevent these, for they may prove fatal. Only those related to the pharmacological actions of anesthetics will be discussed in detail. The classification used here is that of Guedel (1937).

Circulatory Accidents. *Anesthetic Hypertension.* Asphyxia and the release of epinephrine are the two major causes of a sudden rise in blood pressure during the course of anesthesia. The asphyxial rise is more intense when accompanied by struggling and is especially likely to occur during the induction period. The discharge of epinephrine also is apt to occur during induction, due to fear or struggle, and the blood pressure may increase sharply. As anesthesia deepens, hypertension due to epinephrine becomes less and less pronounced. The dangers incident to hypertensive crises lie in the possibility of vascular hemorrhage in persons with diseased vessels, or acute dilatation of the heart in the presence of preexisting myocardial damage. Control of these accidents depends on careful selection of patients, proper management of induction, and prevention of oxygen want and carbon dioxide accumulation.

Anesthetic Hypotension. The principal causes of dangerous hypotension during anesthesia are *hemorrhage* and *shock.* Regardless of the etiological mechanism, the ultimate result is tissue anoxia. Hemorrhage is mainly a surgical problem. Until transfusion can be performed, intravenous administration of fluids and the inhalation of a high percentage of oxygen are helpful. Carbon dioxide may also be given because it increases the tone of arterial walls. Indeed, the hypotension produced experimentally in anesthetized dogs hyperventilated mechanically results from the combined effects of the anesthetic and the loss of CO_2 (Seevers and coworkers, 1940).

Shock, whether due to the anesthetic or to the surgical procedure, has the same underlying pathological physiology. The mechanism of shock and the usual measures employed in treating it are described elsewhere (page 586). It can be prevented by avoiding anesthesia deeper than is absolutely necessary, by conserving body heat and moisture, by maintaining an optimal CO_2 level, by allowing sufficient oxygen at all times, and by treating the tissues as gently as possible.

Ventricular Fibrillation. This arrhythmia is more fully discussed under chloroform anesthesia. Although chloroform is the chief offender and ethyl chloride is next in order, every anesthetic is potentially dangerous in this regard. Ventricular fibrillation is most likely to occur in the induction phase, and results not only from the direct action of the anesthetic agent on the heart but also from the discharge of epinephrine and overactivity of the sympathetic nervous system. Delirium or operative stimuli in the second stage are added precipitating factors. The respirations cease almost immediately after the pulse, and this respiratory arrest should not be mistaken for a temporary apnea or the cardiac state will remain unrecognized for some time. Although treatment is usually futile, immediate artificial respiration and intratracheal oxygen are indicated. Cardiac massage through the diaphragm may be performed. The danger of ventricular fibrillation is reduced by proper preanesthetic medication, by smooth and rapid induction, and by avoidance of premature surgical procedures and the use of epinephrine for any purpose during early anesthesia.

Respiratory Accidents. *Respiratory arrest* during anesthesia may occur for a variety of reasons. The seriousness of the apnea depends upon the causative factors and the stage in which it occurs. Apnea of central origin observed in the induction phase or late in anesthesia has been discussed under the stages of anesthesia. Central respiratory arrest is occasionally due to increased intracranial pressure. In patients who have elevated cerebrospinal fluid pressures or brain tumors, one should be cautious in the use of opiates or anesthetics which further increase intrathecal pressure.

Respiratory arrest also occurs from *breath holding* which is seen only in stage I and is due to emotional disturbance or laryngeal irritation. *Pharyngeal spasm* is more troublesome, appears at the end of stage I, and may persist intermittently through stage II. Attempts to maintain an airway or force oxygen past the obstruction usually fail, and one must wait until the CO_2 concentration rises and the oxygen content of the blood falls sufficiently to break through the spasm and stimulate breathing. *Laryngeal spasm* is the result of reflex adduction of the vocal cords due to their direct irritation or to painful stimuli elsewhere. Laryngeal spasm from direct stimulation disappears in plane ii. Spasm of the vocal cords secondary to painful stimuli has been discussed.

If the muscles of the lower jaw are sufficiently relaxed, the base of the tongue may obstruct respiration by falling against the posterior wall of the pharynx. This has been misnamed *tongue swallowing.* It is observed rarely during the first two stages of anesthesia but may occur after the patient is returned to his bed if he is placed in the supine position. The danger may be circumvented by the use of a pharyngeal airway or by holding the lower jaw forward. Another form of mechanical respiratory obstruction is due to *aspiration of débris.* Foreign objects may lodge in the pharynx, trachea, bronchi or, if liquid, in the lungs. Teeth, sponges, instruments, and blood, pus or mucus are the common offenders. Secretion of mucus should be controlled by adequate doses of atropine or scopolamine. Postural drainage and suction may be employed to prevent aspiration of blood or pus. Endotracheal anesthesia with suction is the best method of avoiding aspiration during lung surgery for abscess or bronchiectasis. The aspiration of *vomitus* is usually avoidable. Reflex vomiting is more likely to occur during lower stage II anesthesia than at any other time. The stomach should be empty before inducing anesthesia, and if one is in doubt it is imperative that a gastric tube be passed; but even this cannot be depended upon to remove large particles. Aspiration usually occurs when emesis follows a long period of retching and breath holding. In spite of an alert anesthetist, the vomitus filling the pharynx may be drawn down into the trachea. Postanesthetic vomiting is less dangerous but must be properly treated. Carbon dioxide may be inhaled to hasten emergence from anesthesia and thus lessen the likelihood of vomiting. The pulmonary complications from aspirated vomitus are often severe and may be fatal.

Miscellaneous Accidents. *Massive collapse of the lung* secondary to anesthesia is usually caused by shallow respiration and bronchial obstruction, particularly from mucus. Atelectasis is due to complete absorption of gases by the blood flowing through the lung distal to an occlusion of a main bronchus, and occurs within a few minutes. It may not be noticed if a closed system with high oxygen tension is being used. As soon as the anesthetic is stopped, however, cyanosis and dyspnea are apparent and physical examination reveals evidence of pulmonary collapse. Atelectasis often results in serious postoperative pneumonia. Prevention depends upon maintaining sufficient depth of respiration by inhalation of CO_2 if necessary, and vigorous hyperpnea induced with CO_2 at the end of each operation in which breathing has been shallow. In treating fully developed atelectasis, oxygen and carbon dioxide should be administered for an hour or longer, and direct bronchoscopic removal of the mucus plug may be attempted if early evidence of improvement is not forthcoming.

Convulsions may occur occasionally under anesthesia. (*See* reviews by Rosenow and Tovell, 1936, and Lundy, 1937.) Oddly, most of them have taken place under ether, and the term "ether convulsions" has arisen to describe this phenomenon. A dramatic description of the convulsion is given by Hudson (1936). The convulsion is epileptiform in character and usually develops in children with infectious or toxic processes and high fever. Of 144 cases reviewed by Lundy (1937), 53 per cent of the patients were children. The convulsion may supervene in any stage. Anoxemia is not the cause, for the attack may occur in the presence of a high oxygen tension in the blood. Nor is ether alone the cause. Experiments on animals have indicated that clinical convulsions possibly may result from a combination of anesthesia, fever and factors causing metabolic acidosis and elevated carbon dioxide tension in the blood (Cassels, Becker and Seevers, 1940). The intravenous injection of short-acting barbiturates has been reported to control ether convulsions.

Postanesthetic fever is rare and proof that the anesthetic is to blame is lacking. A high temperature reaching 108 to 110 F. may develop several hours after operation; usually no cause is found for it, and the patient dies despite therapy.

Cerebral asphyxia may result in irreversible cortical damage if prolonged beyond the limit of tolerance of the nerve cells for anoxia. The small pyramidal cells of the cortex can withstand oxygen lack for only six to eight minutes. Cortical injury is permanent and results in many neurological and psychiatric syndromes, including parkinsonism, athetoid movements, mental defects, idiocy and decorticate rigidity. Nitrous oxide is the worst offender because it often necessitates limitation of oxygen. (*See* Courville, 1936, 1938, and 1939, for review; also Gildea and Cobb, 1930, for effects of experimental anoxia on the cortex.)

Anesthetic Explosions. Explosions are among the most serious accidents that can occur in anesthesia. Oxygen, carbon dioxide, nitrous oxide and chloroform are noninflammable. Oxygen is important in explosions, however, because it supports combustion. Oil should not be used on the valves or gauges of oxygen tanks because the oil may ignite when suddenly exposed to high oxygen pressure and cause a violent explosion. Oxygen also must not be mixed in the same cylinder with ethylene. It is a myth that carbon dioxide reduces the inflammability of anesthetic agents as used clinically. Although chloroform is not inflammable, it is oxidized in the presence of an open flame to phosgene gas (carbonyl chloride, $COCl_2$), chlorine and hydrochloric acid, all of which cause pulmonary irritation, cough and dyspnea. Collapse may even ensue and phosgene in concentrations as low as 1:40,000 is said to be capable of causing death from pulmonary edema.

The inflammable and explosive agents used in anesthesia are ether, ethylene, cyclopropane, divinyl oxide and ethyl chloride. Fortunately, the incidence of anesthetic explosions is low and only two deaths from this cause occurred in over two million anesthesias (Woodbridge, 1939). The precautions concerning the use of open flames and the cautery are mentioned under the particular anesthetic agents. Electric sparks are the cause of most accidents, and are mainly static in origin. Static sparks originate from friction in opening and closing valves, in the rubber breathing bag, in the flowing of dry gases through the anesthetic apparatus, etc., and are always a potential source of danger. Static electrical discharges can be prevented, to some degree, by elevating the humidity of the air in the operating room to 65 per cent or more. Complete and suitable grounding of the anesthetic apparatus, patient and surgical team is also effective but often difficult or impractical, necessitating conductive floors and shoes, and drag chains from tables and anesthesia machines. A technic of high resistance intercoupling (Horton intercoupler) which provides safety from anesthetic explosions due to static sparks has also been devised (Woodbridge, Horton and Connell, 1939). Cotton material (not wool or silk) for clothing and drapes should be used, and towels and drapes may be rinsed, after laundering, in 0.5 per cent calcium chloride solution in order to decrease the static potential which can be induced on them by friction. The wetting of the anesthetic breathing bag and hose before use is also an important safeguard against static ignition in the apparatus. An explosive anesthetic mixture should not be flowing through the apparatus at the time the mask is applied to the patient's face, and the anesthetist should not remove the mask more frequently than is absolutely necessary.

Anesthetic Deaths. It is desired only to emphasize that the anesthetic is not always the cause of death. Indeed, the cause may be extremely difficult to determine. There are several quite famous historical examples to illustrate that death may be due to causes other than anesthesia. The experience of Sir James Simpson about to perform his first operation under chloroform has already been mentioned. Death has even occurred in a patient who was breathing air through a gauze mask in the belief that he was receiving chloroform. The tendency to attribute death under anesthesia to ill-defined causes such as "anesthetic shock" and "status thymolymphaticus" is rapidly disappearing. Improvement in anesthetic technic and careful selection of patients have resulted in a marked decrease in mortality. Also, more frequent and careful autopsies have aided in discovering the real causes of death during anesthesia.

PROPERTIES OF THE IDEAL ANESTHETIC

The qualities desired in an ideal anesthetic have been well summarized by Seevers and Waters (1938) who point out that the desires of four individuals must be satisfied as follows: The *patient* desires not only rapid and pleasant induction with an anesthetic which is non-irritating and free from unpleasant odor, but also a recovery period which is free of discomfort. The *surgeon* would be satisfied if the agent were not explosive, if it were capable of producing complete muscular relaxation and did not increase capillary bleeding. The *anesthetist* desires an anesthetic to have a wide margin of safety, to be excreted from the body entirely unaltered, to cause a minimum of functional or organic injury during and following its use, to be sufficiently potent so that a high percentage of oxygen may be employed in the anesthetic inhalant mixture at all times, and to diffuse sufficiently rapidly to allow moment to moment control of the depth of anesthesia. The *manufacturer* is interested in having an anesthetic which can be produced simply and inexpensively, purified without difficulty and stored without undergoing chemical changes.

No known anesthetic fulfills all the qualifications listed. Seevers and Waters are inclined to believe that the ideal anesthetic should be a gas. At least, agents such as barbiturates and tribromethanol which depend for their rapidity and lability of action on renal elimination or destruction in the body are not sufficiently safe to be widely serviceable as general anesthetics. Were it a more potent gas, nitrous oxide would qualify as the ideal anesthetic.

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CHAPTER 5

GENERAL ANESTHETICS

I. ETHER AND CHLOROFORM, DIVINYL ETHER, ETHYL CHLORIDE AND TRICHLOROETHYLENE

The general anesthetics to be discussed in the following pages are the volatile liquids—*ether, chloroform, divinyl ether, ethyl chloride* and *trichloroethylene;* the gases—*nitrous oxide, ethylene, cyclopropane* and *acetylene;* and the basal anesthetic, *tribromethanol.*

Advantages and Uses of General Anesthesia. General anesthesia is essential when complete unconsciousness and adequate relaxation of muscles are desired, and when movement of the patient may imperil the success of the operation. It has the advantage over spinal or local anesthesia of removing the factors of anxiety and fear. General anesthesia is often necessary in abdominal operations of an exploratory character when the nature of the subsequent surgical procedures cannot be fully anticipated. Furthermore, it is necessary in thoracic surgery where spinal anesthesia is not safe. Finally, it is useful in states of extreme excitability of the central nervous system, as in strychnine convulsions, tetanus, etc. The intravenous use of the soluble barbiturates has largely replaced the inhalation anesthetics for treatment of these convulsive states.

ETHER AND CHLOROFORM

Ether continues to be the most widely used general anesthetic. It is the standard with which all newer anesthetics are compared and therefore its actions will be considered in detail. Chloroform, because of its toxicity, has largely disappeared from use. It is of great historical interest, however, and in some parts of the world, especially in the tropics, is still widely employed. Because of these facts and also for the reasons that chloroform contrasts sharply with ether in many ways and teaches a number of important points about general anesthesia, chloroform and ether will be discussed together.

Chemistry and Preparations. The chemical properties of ether, $C_2H_5OC_2H_5$, and chloroform, $CHCl_3$, are too well known to warrant discussion. It may be stated, however, that numerous studies on the relationship of chemical structure to pharmacological action indicate that the ethyl radicle is apparently potent and relatively safe for the production of central nervous system depression, and that the introduction of ether groups enhances anesthetic potency. These facts are exemplified in ethyl ether which combines both structures. The inclusion of halogens, chlorine or bromine, in the alkyl group of an anesthetic increases the depressant power, but at the same time the toxicity for certain organs, particularly the heart and liver, is increased. Chloroform is a pertinent example. One interested in the extensive and important question of the relation between chemical structure of anesthetics and their clinical actions and usefulness is referred to Shonle (1932) and Killian (1934).

Ether, U.S.P., B.P., contains from 96 to 98 per cent of $(C_2H_5)_2O$, the remainder consisting of alcohol and water. The U.S.P. specifies that ether to be used for anesthesia must be preserved only in small, well-closed containers, and is not to be used for this purpose if the original container has been opened longer than 24 hours. It has been demonstrated, however, that U.S.P. ether supplied in large metal containers stoppered with cork does not deteriorate over a period of many weeks when the containers are opened repeatedly for transfer of the contents to small anesthetic cans, but well stoppered in the interim. Such ether is suitable for anesthesia and the cost is materially reduced (Gold and Gold, 1934; Dooley, 1935; Morrison, 1938; Hediger, Chenoweth and Gold, 1940).

Chloroform, U.S.P., B.P., contains between 99 and 99.5 per cent of $CHCl_3$, the remainder consisting of alcohol. Care should be taken not to vaporize chloroform in the presence of a naked flame, because of the production of noxious gases.

Pharmacological Actions

Central Nervous System. The typical action of the methane anesthetic series and the probable mechanisms of this action have already been discussed. Also, the signs and symptoms of each stage of anesthesia have been described. Certain additional points, however, should be stressed. Chloroform is the most potent of all the inhalation anesthetics, being over three times more depressant than ether per unit of concentration in the blood. Both ether and chloroform are 100 per cent anesthetics inasmuch as they carry the patient through all planes of surgical anesthesia to respiratory arrest from any level of reflex excitability without the intervention of oxygen deprivation or preanesthetic medication (Figure 4). None of the other inhalation anesthetics produces quite the same degree of muscular relaxation during stage III as do ether and chloroform, and some are quite inferior in this respect. To obtain complete abolition of spinal reflexes and muscular relaxation sufficient for abdominal surgery, small amounts of ether are often used to supplement nitrous oxide, ethylene or cyclopropane.

Respiration. *Local Actions.* Chloroform is more irritating than ether to the skin and mucous membranes. As an anesthetic, however, ether is more irritating to the respiratory passages because a concentration of ether three times higher than that of chloroform in needed in the inspired air. Thus ether causes greater stimulation of bronchial secretions and is often contraindicated in patients with pulmonary disease. Both chloroform and ether also markedly stimulate the flow of saliva during induction of and recovery from anesthesia, but salivation is inhibited during the deeper planes of surgical anesthesia.

Systemic Actions. The character of respiration in each stage of ether anesthesia has already been presented, as well as the types of respiratory arrest which may occur. It is well to reemphasize the fact that most acute anesthetic deaths occur in stage II, and are due to irregular breathing which results in sudden changes in the concentration of anesthetic in the body.

Ether and certain other volatile anesthetic agents directly stimulate the medullary respiratory centers, despite the concurrent depression of other levels of the central nervous system. Thus there is an increase in respiratory minute volume during planes i and ii of stage III (Figure 3). Below lower plane ii, both ether and chloroform depress respiration and raise the threshold of excitability of the respiratory center to carbon dioxide and to afferent stimuli. Cheyne-Stokes respiration is sometimes seen when chloroform is used but is rare with ether. In the paralytic stage, breathing stops before the heart beat ceases with both chloroform and ether. Functionally, however, the cardiovascular system becomes inefficient during chloroform anesthesia before respiration actually ceases.

Heart and Circulation. *Ether.* The cardiac rate is increased during the phase of induction when ether is used. This is due mainly to the release of epinephrine. The blood pressure, after a preliminary rise during the induction period, remains quite normal during surgical anesthesia with ether, even if anesthesia continues for some time. In plane iii, however, 15 minutes of ether anesthesia may cause as great a fall in blood pressure as two hours in the second plane. This is due to the depression of smooth and skeletal muscle tone and a consequent loss of support to the circulation. Inasmuch as the great majority of surgical operations do not require third plane anesthesia, ether is relatively innocuous to the circulation when it is expertly administered.

Ether causes some peripheral vasodilatation, mainly by a direct action but in part through mild central vasomotor depression. The blood flow through peripheral arteries is definitely enhanced during light ether anesthesia (Mann and coworkers, 1935). The skin, especially that of the face, is red, and the cerebral and meningeal vessels, whose responses often parallel those of the face, are also dilated. The cerebrospinal fluid pressure, as a result, rises (Myerson and Loman, 1932). In the paralytic stage, the vasomotor center is seriously depressed and the blood pressure falls due to peripheral vasodilatation. The heart remains unimpaired even at the time when respiration stops. The circulation is inefficient, however, because the peripheral vascular depots are flooded. The excellent status of the heart at the stage of respiratory failure allows for the revival of the patient by prompt restoration of pulmonary exchange. This can be accomplished by artificial respiration, or by inserting a small catheter into the trachea and delivering an adequate flow of oxygen directly to the lungs.

Ether can depress the heart directly but only with concentrations higher than those obtainable during anesthesia. For example, the lethal blood concentration of ether is about 160 mgm per cent. The perfused, isolated oxygenated heart, on the other hand, is capable of withstanding an ether concentration of approximately 450 mgm per cent, nearly three times that necessary to cause respiratory failure. In this regard, ether contrasts sharply with chloroform. A concentration of chloroform of 10 mgm per cent, if prolonged, is demonstrably injurious to the heart and 15 mgm per cent may cause cardiac arrest. These harmful concentrations are exceeded in order to obtain clinical anesthesia. The evidence indicates that chloroform is 25 to 30 times more toxic to the heart than is ether.

Despite the absence of clinical evidence of disturbed cardiac function during ether anesthesia, electrocardiographic changes may be noted (Kurtz and coworkers, 1936). The pacemaker may be shifted downward, and extrasystoles may occur. The latter are auricular rather than ventricular in origin, however, and the ominous types of arrhythmia seen with chloroform and toxic concentrations of cyclopropane do not occur. Ether also differs from cyclopropane and chloroform in that it does not sensitize the automatic tissue of the ventricle to epinephrine and related sympathomimetic amines (*see* Orth and coworkers, 1939). Arrhythmias due to ether are more likely to occur early in the course of anesthesia whereas arrhythmias due to cyclopropane are more likely to occur in deeper planes of anesthesia (Table 2).

Chloroform. The effects of chloroform on the heart and circulation differ markedly from those of ether. With the onset of surgical anesthesia induced by chloroform, the blood pressure gradually and continuously declines. At the end of one hour, the pressure may reach such a low level that anesthesia can no longer safely be continued. Cardiac output is uniformly decreased by chloroform anesthesia whereas it is significantly increased when ether is used (Blalock, 1927, 1928). Even under the most favorable circumstances, chloroform cannot be used for much longer than one hour. Three factors are involved in the cardiovascular action of chloroform. Chloroform causes a direct depression of the vasomotor centers and, as a result, peripheral vessels are dilated, especially those in the splanchnic area. Chloroform also has a direct depressant action on the musculature of blood vessels. Lastly, chloroform is directly depressant to the myocardium. The heart muscle is further injured by anoxia due to depression of respiration and progressive hypotension.

With the approach of the paralytic stage of anesthesia, the blood pressure is therefore quite low. Although the effects of vasomotor paralysis and cardiac incompetence dominate the circulatory picture until death, the heart remains beating after respiration has ceased. The heart beat is quite feeble and despite the fact that breathing actually stops first, functionally the circulation fails before the respiration.

Ventricular Fibrillation from Chloroform. Sudden syncope due to cardiac arrest may occur during the induction phase of chloroform anesthesia, particularly when administration is faulty or surgical maneuvers are started before anesthesia is sufficiently deep. For many years it was believed that the asystole was vagal in origin, but it is now known that ventricular fibrillation is the cause. The fundamental experiments in this field were performed on animals by Levy (1911, 1913, 1914) who demonstrated that chloroform sensitizes the heart so that it is more susceptible to factors precipitating ventricular arrhythmias and fibrillation. He found that fatal ventricular fibrillation could be induced in animals under light chloroform anesthesia by the injection of epinephrine, and that vagal resection and atropinization were not preventive measures. Levy also demonstrated that deep anesthesia offered protection against arrhythmia and that ether never precipitated ventricular fibrillation.

Sudden death during the induction phase of chloroform anesthesia is the most common type of cardiac accident noted when this agent is used. The clinical diagnosis can be made only if the anesthetist has his fingers on the pulse of the patient at the moment the arrhythmia occurs. A sudden decrease in cardiac rate from normal to zero "between two heart beats" is presumptive evidence of ventricular fibrillation. Several factors may combine to cause the fatal fibrillation. Irritation of the upper respiratory passages may initiate a trigeminocardiac reflex mediated from the brain stem through the spinal cord and stellate ganglia to the heart by way of the cardiac sympathetic nerves. This tends to cause ventricular tachycardia and extrasystoles. The discharge of epinephrine from the adrenal medulla due to fear or painful stimuli may act on a chloroform-sensitized myocardium to precipitate arrhythmia. The direct action of chloroform on the myocardium reduces the refractory phase of heart muscle, increases the irritability of the ventricle and lowers the threshold for the deleterious effects of epinephrine and sympathetic nerve impulses. Stimulation of the stellate ganglia in animals under light chloroform anesthesia, for example, will cause ventricular fibrillation. Lastly, an increased tension of carbon dioxide in the blood enhances the possibility of chloroform-induced fibrillation of the ventricles. Due to the irregular respiration and periods of apnea of a stormy induction, both high carbon dioxide and high chloroform concentrations are apt to coincide.

Although chloroform causes ventricular fibrillation much more readily than does any other anesthetic agent, ethyl chloride is also capable of initiating the arrhythmia. Even when clinical observation of the patient under chloroform anesthesia reveals no abnormalities of cardiac function, electrocardiographic evidence of ventricular irregularities may be seen. Hill (1932) restudied the effects of chloroform on the human heart and has confirmed clinically the aforementioned experimental findings of Levy. About 50 per cent of all persons under chloroform anesthesia manifest the ominous type of multiple focus ventricular tachycardia (Figure 5) which precedes ventricular fibrillation. The disturbance is transient, disappears as anesthesia deepens, and is not detectable clinically.

Gastro-intestinal Tract. *Nausea and vomiting* appear especially during recovery from anesthesia, but may occur during induction. The mechanism is central rather than local, but may be due in part to irritation of the stomach from swallowed vapors of ether or chloroform. Postoperative vomiting is a complication which may prove harmful and which the surgeon attempts to avoid by careful selection of the anesthetic. With ether, the incidence of nausea or vomiting approximates 57 per cent, as reported by Waters (1936) from a study of 10,600 administrations of anesthesia. In this same series, the incidence of nausea or vomiting for other agents was as follows: cyclopropane, 39 per cent; ethylene, 33 per cent; nitrous oxide, 23 per cent.

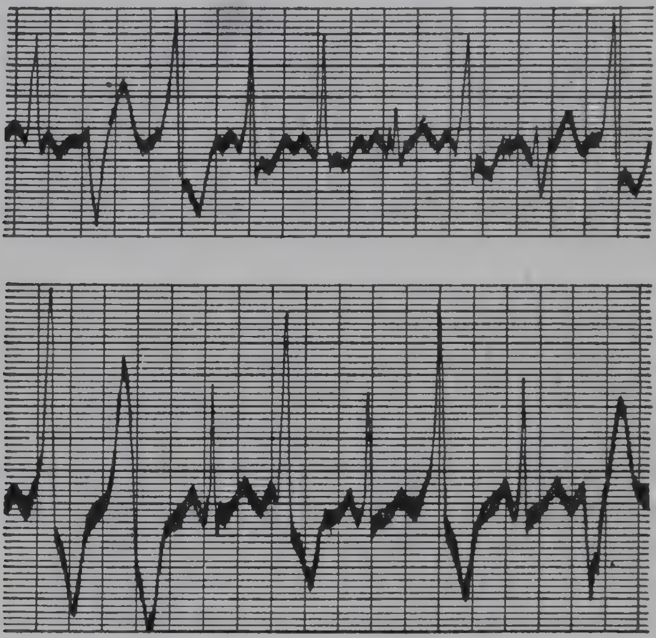

FIGURE 5. *The effect of chloroform anesthesia on the human heart as noted in the electrocardiogram.*

Upper tracing: Lead II, male, aged 56. Seventeen minutes after the induction of chloroform anesthesia, the heart rate is 142 per minute and no normal ventricular complexes are evident. All complexes are ventricular extrasystoles of diverse origin. Rhythmic P-waves are visible before many of the ventricular beats.

Lower tracing: Lead II, female, aged 38. Twenty-six minutes after the induction of chloroform anesthesia, the heart rate is 128 per minute and multiple extrasystoles from both ventricles are present. (After Hill, 1932. Courtesy of the *Edinburgh Medical Journal.*)

Gastro-intestinal tone and movements are considerably inhibited during and for varying periods after surgical anesthesia with ether and chloroform. This may be due to a peripheral action of the anesthetic agents on smooth muscle and its intrinsic autonomic innervation (Miller, 1926). Chloroform is more depressant in this regard than ether. Postanesthetic dilatation of the stomach occurs to some degree in nearly all cases; but occasionally acute and marked dilatation of the stomach may follow general anesthesia. This is a grave complication which necessitates early diagnosis and urgent treatment. The gastro-intestinal atony which follows abdominal operations is only in part the result of the anesthetic. It arises in no small measure from handling of the viscera during operation. Preanesthetic medication with morphine tends to counteract the depression of the gastro-intestinal musculature caused by anesthesia, but atropine nullifies this action of morphine to some degree.

The incidence and severity of postoperative intestinal ileus vary with the type and duration of anesthesia and the nature of the operation. In the series of anesthetic administrations studied by Waters (1936), to which reference has been made, ether caused postoperative distention in 16.5 per cent of 2400 cases. The incidence for other anesthetic agents was as follows: cyclopropane, 13.5 per cent of 5900 cases; ethylene, seven per cent of 1000 cases; nitrous oxide, three per cent of 1300 cases. Usually the small intestine recovers its normal motility within 48 hours after anesthesia. The colon, on the other hand, recovers within a few hours and becomes quite spastic. This results in the accumulation of gas and fluid in the small bowel. Various drugs, including posterior pituitary solution, physostigmine, prostigmine, mecholyl and other choline esters, in addition to enemata and rectal tubes, are used to stimulate peristalsis and relieve the pain of gaseous distention.

Urinary Tract. In man, the flow of urine steadily diminishes during anesthesia with chloroform; this is associated with a declining blood pressure. Urinary flow is also diminished when ether is used, perhaps because of renal circulatory changes or the anhydremia which accompanies ether anesthesia (Barbour and Bourne, 1924). Both ether and chloroform produce some degree of renal irritation but this is more pronounced with chloroform. The incidence of postanesthetic albuminuria is variable. Casts are occasionally found in the urine after anesthesia with either agent. Chloroform anesthesia may be followed by glycosuria due to hyperglycemia. Phenolsulfonphthalein excretion tests indicate a slightly lowered renal function during and for a day or two after ether anesthesia. Renal irritation occurring after ether is transient in patients with normal kidneys. In patients with chronic nephritis, however, serious exacerbations of the disease may result. Chloroform is the more serious offender. To cite but one example, in animals with experimental uranium nephritis, chloroform anesthesia is quite toxic, but ether anesthesia is relatively innocuous (MacNider, 1913). Injury to the kidney arising from chloroform is evident mainly in the tubular epithelium. The effects of anesthesia on the kidney have been reviewed by Mousel and Lundy (1940).

Postoperative retention of urine is fairly frequent after chloroform and ether anesthesia and may require catheterization or the use of drugs to stimulate the atonic urinary bladder.

Uterus. During parturition, uterine activity is only slightly influenced by light anesthesia which is employed intermittently to coincide with the periods of pain. Obstetrical analgesia sufficient to control labor pains may be obtained with a depth of anesthesia which does not interfere with the progress of labor. The use of ether presents some difficulty because of the time interval necessary for induction of ether analgesia. Unless the pains are anticipated, the analgesic effects of the ether may come only after the pain has developed. Ether, however, is very safe and the amnesia for pain which follows each interval of its administration does much to relieve the ordeal. Ether may also be given rectally in oil for obstetrical analgesia and amnesia (Gwathmey and McCormick, 1935). Chloroform is more rapid in action and therefore quickly produces obstetrical analgesia, but is unsafe to use because of its toxic effects on the liver.

During the second stage of labor, ether anesthesia is often employed for normal delivery or low forceps extraction. When properly given to the depth of lower plane i, ether is safe and does not seriously interfere with the forces of labor or the respiration of the infant. With deeper anesthesia, uterine contractions are somewhat slowed and weakened, and labor prolonged. Maximal relaxation of the uterus does not occur until plane iii is reached. All volatile anesthetics easily pass the placental barrier and thus reach the same concentration in the fetal circulation as in the maternal blood.

Metabolic Effects. Most workers are agreed that general anesthetics tend to reduce the serum bicarbonate and pH of the blood. This occurs especially in prolonged anesthesia, and chloroform causes the greatest decrease. The bicarbonate is displaced partly by chloride and partly by an unidentified acid (Austin and coworkers, 1924), possibly phosphoric acid (Stehle and Bourne, 1924) or lactic acid (Ronzoni and coworkers, 1924). Acetone bodies may also appear in the urine after ether or chloroform anesthesia, especially the latter. In diabetes mellitus chloroform anesthesia is particularly dangerous.

Hyperglycemia is a frequent accompaniment of general anesthesia and occurs especially during induction. The blood sugar may rise to a level two or more times higher than normal. Hyperglycemia is probably due to increased glycogenolysis in the liver or to an inhibition of the action of insulin; but the exact mechanism is not settled. The liver glycogen falls coincident with the blood sugar rise. The elevation in blood sugar is markedly reduced by section of the hepatic nerves or by adrenalectomy (Phillips and Freeman, 1933). Hyperglycemia due to ether anesthesia is probably related especially to the secretion of epinephrine and stimulation of the sympathetic nerves to the liver; but a small residual rise in blood sugar occurs during ether anesthesia in completely sympathectomized animals. The elevation of blood sugar after chloroform is more marked and more prolonged than after ether, and may be due in part to a direct action of chloroform on liver cells (Ravdin and coworkers, 1938). As a rule, normal blood sugar levels are again reached within 24 hours after anesthesia.

Liver Damage by Chloroform. Chloroform, like certain other halogenated hydrocarbons, is capable of causing cirrhosis of the liver if given in small repeated doses. The prolonged administration of chloroform anesthesia results in acute fatty degeneration of the liver, and the kidney, heart, and other parenchymatous organs are likewise damaged. Within a few days after chloroform anesthesia, there may develop severe prostration, protracted nausea and vomiting, jaundice and coma. This syndrome, which has been called "delayed chloroform poisoning" and "postanesthetic toxemia," often results in death. It is practically never seen after ether. The upper time limit for safety as regards the liver is about 45 to 60 minutes of chloroform anesthesia, a limit also imposed by the fall in blood pressure caused by this agent. Chloroform is absolutely contraindicated as an anesthetic in patients with hepatic disease and may be said always to injure the liver.

The symptoms of delayed chloroform poisoning develop from the first to the third postoperative day. Thus there may be an asymptomatic interval after recovery from anesthesia. The course of the illness is somewhat similar to that of phosphorus poisoning, because in both are seen the blood, urinary and metabolic changes associated with severe toxic hepatitis or acute yellow atrophy. Jaundice, increased serum bilirubin, bile in the urine, reduction in liver function, increased nitrogen excretion, lowered blood fibrinogen and the appearance of leucine and tyrosine in the urine are some of the more prominent findings. The hemorrhagic tendency which occurs is due to the failure of prothrombin formation by the injured liver (see page 1296). Death usually occurs on the fourth or fifth day, and autopsy reveals degeneration and necrosis of liver tissue most marked around the central veins—a finding typical of chloroform poisoning. Recovery occurs without residual liver damage.

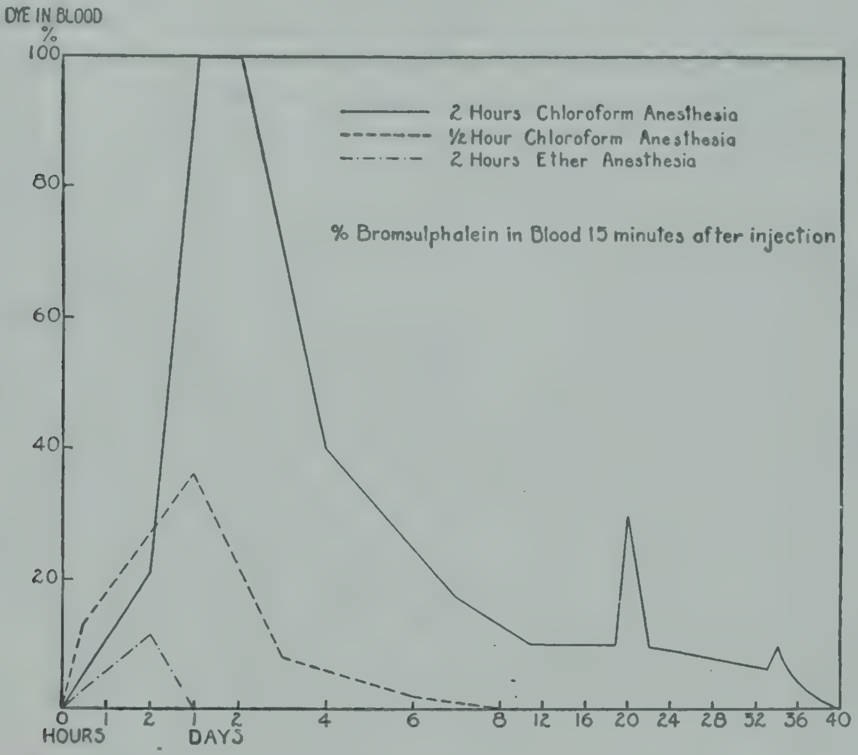

FIGURE 6. *The effect of chloroform and ether anesthesia on the hepatic function of dogs as measured by bromsulfalein dye excretion tests.*

Control figure at zero time. Before anesthesia the liver removes all the injected dye from the circulation within 15 minutes. Observe that only 30 minutes of chloroform anesthesia cause functional impairment of the liver detectable for eight days; two hours of chloroform anesthesia, for 40 days. In contrast, ether anesthesia for two hours causes only slight alteration in hepatic function, no longer evident after 24 hours. The secondary rises occurring late in the two-hour chloroform curve are associated with lipemia. Note the change in time scale. (After Rosenthal and Bourne, 1928. Courtesy of *The Journal of the American Medical Association.*)

The experiments of Rosenthal and Bourne (1928), in which bromsulfalein was used to study the effects of anesthesia on the hepatic function of dogs, show clearly the differences between chloroform and ether. The livers of normal dogs excrete into the bile nearly 100 per cent of the intravenously injected dye within fifteen minutes. When chloroform anesthesia is given for only one-half hour, impaired elimination of dye is detectable for eight days. If the chloroform is administered for two hours, impairment of dye excretion lasts for six weeks. On the other hand, full ether anesthesia causes only slight retention of dye, and excretion is quite normal on the second postanesthetic day (Figure 6). These functional tests are quite sensitive and correlate well with the known histologic changes seen in the liver after varying periods of inhalation of chloroform. Even after several hours of ether anesthesia, cytological evidence of liver damage is not apparent.

The hepatic changes induced by chloroform can be prevented in some measure by a high carbohydrate, high protein and low fat diet prior to anesthesia and by avoiding anoxia. Conversely, starvation and a high fat diet render the liver more susceptible to damage, and anoxia increases the injury caused by chloroform. Liver glycogen probably offers in itself no specific protection but rather insures, when it is plentiful, a concomitant absence of fat in the liver cells. It may also exert a "protein-sparing" action. The best protection appears to be afforded by a plenitude of protein stored in the liver (Goldschmidt, Vars and Ravdin, 1939).

Miller and Whipple (1940) also have emphasized the rôle of adequate protein stores in the body in protecting against liver damage by chloroform. For example, they have shown that 15 to 20 minutes of chloroform anesthesia in dogs depleted of protein (by low protein diet alone or combined with bleeding or plasmapheresis) is frequently fatal and causes extensive hyaline necrosis of the liver and the typical picture of chloroform poisoning. Control experiments in dogs without protein depletion indicated that 90 minutes of chloroform anesthesia could be tolerated with but little liver injury. That protein is also protective against hepatotoxic agents other than chloroform is suggested by the experiments of Messinger and Hawkins (1940) who found that liver injury produced by arsphenamine in dogs fed a protein diet was trivial and promptly repaired. A carbohydrate diet was somewhat less beneficial than protein in this respect and fats proved markedly deleterious. Also, fat-fed animals with severe intoxication induced by arsphenamine showed definite improvement when the fat diet was changed to protein. It is thus clear that the older concept concerning the protective action of carbohydrates on the liver must be modified to include protein. It is also suggested by the experiments cited that, in the face of established acute liver injury, a diet of protein as well as carbohydrate may prove of value. The mechanism by which protein protects the liver requires elucidation, but it has been suggested that protein may exert a direct protective action on liver cells or allow rapid regeneration of liver tissue, *pari passu* with injury (*see* discussion of Goldschmidt and associates, 1939).

Blood. The acetonemia, reduction in plasma bicarbonate, and the hyperglycemia incident to general anesthesia with ether and chloroform, as well as the marked alterations occurring in chloroform poisoning, have already been mentioned. The *formed elements* of the blood are not directly affected by ether anesthesia, but the red and white blood cells and hemoglobin values may be secondarily altered by changes in *plasma volume* and many other factors incident to the anesthesia and operative procedure, including a reduction in the size of the spleen. Ordinarily there occurs some reduction in plasma volume and this, combined with contraction of the spleen, causes a proportionate rise in blood viscosity, red blood cell count and hemoglobin (Barbour and Bourne, 1923; Searles and Essex, 1936; Bollmann, Svirbely and Mann, 1938; Searles, 1939). Stewart (cited by Beecher, 1938), employing the Gregersen dye method, found that during ether anesthesia in man the plasma volume diminished nearly 15 per cent, concomitant with an increase of extracellular fluid volume of over seven per cent. McAllister (1938) has observed a similar reduction of plasma volume in dogs under ether anesthesia.

Coagulation time may be shortened by ether anesthesia (Searles, 1939), but is apparently unaffected by chloroform. Although *hemolysis* of red corpuscles by ether and chloroform can be observed in the test tube, the phenomenon is not seen with the low concentrations necessary for anesthesia. It certainly has not been definitely proved that ether or chloroform hemolyzes red blood cells during clinical anesthesia, as is believed by some. If the patient's hemoglobin value is below 50 to 60 per cent, however, general anesthesia may be an unsafe procedure. A poor hemoglobin content of the blood makes the patient a poor surgical risk. General anesthesia, especially with chloroform, introduces the elements of asphyxia, low blood pressure, and possible damage to red blood cells, all of which are undesirable factors in an anemic individual. The relation of anemia to the appearance and detection of cyanosis is discussed on page 83.

The *white blood cells* are increased in number during ether anesthesia; this causes a rather striking polymorphonuclear leukocytosis. The total number of leukocytes may be increased two- or three-fold and may not return to normal levels for three or more days. These alterations are not peculiar to ether anesthesia, but also occur with other general anesthetic agents, particularly cyclopropane. The mechanism is not fully understood.

Absorption, Fate and Excretion. Ether and chloroform are absorbed almost instantaneously from the pulmonary epithelium, and both are excreted almost quantitatively by the same channel. The total amount absorbed and the rate of excretion are discussed in the following section. The diffusion of the volatile anesthetic agents into and out of the body is purely a physical process, and follows the laws of the passage of water-soluble vapors and gases across permeable membranes.

More chloroform is carried in the blood by the red corpuscles than by the plasma (McCollum, 1930). It is apparently loosely combined with cell lipids. Ether, on the other hand, is more equally distributed between plasma and cells.

Ether is not oxidized in the body, and over 90 per cent of it can be recovered in the exhaled air. Chloroform, on the other hand, is decomposed to a limited extent by the tissues but the degree of this decomposition is practically negligible. A small fraction of both ether and chloroform is excreted in the urine, milk, sweat and other body fluids. The fraction of ether not found in the expired air can be accounted for by extrapulmonary excretion.

Upon discontinuance of anesthesia, the amount of ether and chloroform in the blood is reduced by half within five minutes. The elimination of the remainder is naturally much slower. Traces of ether can be detected two hours after the cessation of anesthesia, but after four hours this is no longer possible. The inhalation of carbon dioxide greatly enhances the rate of excretion of the anesthetic (Figure 7). When chloroform is used, traces are detectable seven hours after anesthesia has ceased and often for as long as twenty-four hours.

General Principles Governing the Transfer of Anesthetic Vapors and Gases. In the last analysis, the degree of anesthesia depends on the concentration of anesthetic agent in the tissues of the central nervous system. This in turn depends on the concentration in the blood, and the latter is controlled by several factors, particularly the anesthetic concentration in the inspired air. The factors controlling the onset and maintenance of surgical anesthesia with ether and chloroform apply as well to all the anesthetic vapors and gases, and the description to be given here does not differ in any important respect for any particular agent.

Five conditions are involved in passage of the anesthetic from the container into the patient's central nervous system (Guedel, 1937). These are as follows: (1) the partial pressure of the anesthetic in the inspired air; (2) the respiratory minute volume; (3) the permeability of the alveolar membrane; (4) the circulation velocity through the lungs; (5) the circulatory volume to different tissues of the body. These factors and their bearing on induction and depth of anesthesia may now be considered.

(1) *Partial Pressure of the Anesthetic Agent.* As previously stated, the anesthetics exist in the blood and body fluids mainly in physical solution and obey the laws governing

the absorption of gases by fluids. The alveolar membrane allows the free passage of volatile anesthetic agents in both directions, and the diffusion is always in the direction of the lower concentration, that is, the lower partial pressure. When anesthesia is first induced, the absorption into the blood is quite rapid because there is a steep concentration gradient downward from the alveolar air to the blood. As anesthesia is continued, this gradient naturally becomes less steep because the blood and tissues are approaching equilibrium with the alveolar air. The diffusion rate is therefore slower. When equilibrium is finally obtained, the diffusion gradient has practically disappeared because the partial pressures of the anesthetic in the tissues and inspired air are nearly equalized, at which point diffusion almost stops. The reverse process occurs when the administration of anesthesia ceases. The air in the lungs now contains a very low partial pressure of the anesthetic, and the diffusion gradient is therefore outward from the tissues to the exhaled air. At first, this outward diffusion gradient is steep, allowing rapid excretion and emergence from anesthesia. As the concentration gradient becomes less steep, diffusion proceeds more slowly. The final elimination of anesthetic, therefore, is quite slow.

The partial pressure of the anesthetic vapor in the inhaled air is of much greater importance in determining speed of induction and depth and safety of anesthesia than is the absolute amount of anesthetic used (Haggard, 1924). To illustrate this point, the fact may be recalled that it is common experience to see one patient inhale and again exhale many ounces of ether in the course of a prolonged operation, without obtaining deep anesthesia; on the other hand, a second patient may be rapidly precipitated into dangerously deep anesthesia by inhaling only a few cubic centimeters of the same anesthetic given as a concentrated vapor.

(2) *Respiratory Minute Volume.* The speed of induction and emergence also depends on the respiratory minute volume. The difficulty of induction due to morphine-induced respiratory depression has been described (page 37). Respiratory depression not only decreases the amount of anesthetic inhaled per unit of time, but also, if breathing is shallow, lessens the extent of the alveolar surface exposed to the anesthesia. Conversely, if respiration is made deeper or faster, as occurs when carbon dioxide is administered, diffusion is enhanced and induction or emergence is speeded (Figure 7).

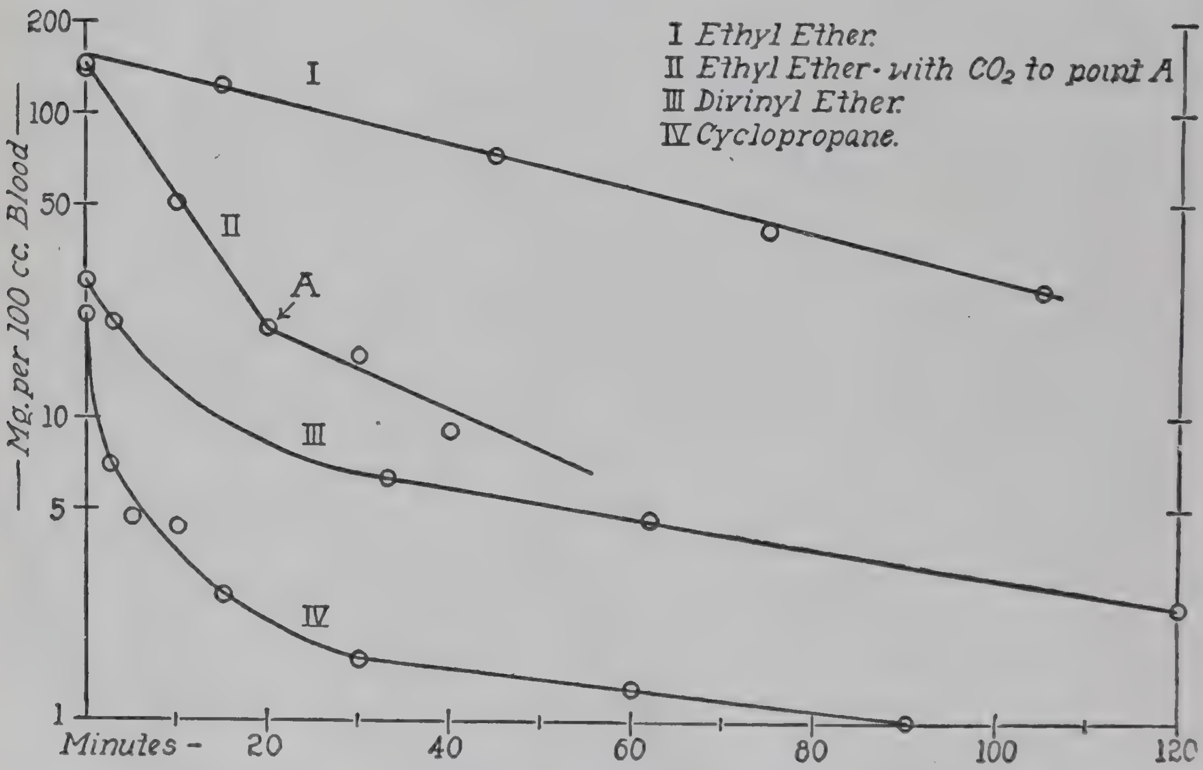

FIGURE 7. *The elimination of anesthetics from the blood.*

Experiments performed on dogs; blood concentration of anesthetics plotted on a logarithmic scale against the time in minutes. Note the more rapid initial excretion of divinyl ether and cyclopropane in comparison with ethyl ether. Observe also that the inhalation of carbon dioxide hastens the elimination of ether from the blood at the termination of anesthesia. (After Ruigh, 1939. Courtesy of the *Proceedings of the Society for Experimental Biology and Medicine.*)

(3) *Permeability of the Diffusion Surface.* The diffusion rate of anesthetics into the blood depends not only on the partial pressure of the gas and the respiratory minute volume, but also on the ability of the alveolar membrane to allow the ready passage of the gas through it. Ordinarily, the alveolar membrane allows free diffusion of gases in both directions. The usual feature encountered in clinical anesthesia which tends to alter the permeability of the normal aveolar membrane is the secretion of mucus. Obstructed alveoli offer an appreciable obstacle to the passage of gases, and higher partial pressures of anesthetic vapors are then needed to obtain the same speed of onset and depth of anesthesia.

(4) *Circulation Velocity.* The circulatory velocity of the blood is not particularly important under most circumstances, except in regard to the rapidly acting anesthetics such as nitrous oxide, ethylene and cyclopropane. Even then, it determines only the speed of induction. All the blood of the body is said to pass through the lungs in slightly more than one minute, and at least one and usually two such circuits must be made in the presence of high partial pressures of the gases before full brain saturation and surgical anesthesia can occur.

(5) *Rate and Volume of Blood Flow through the Brain and Other Tissues.* The abundant blood supply of the brain assures that this organ becomes saturated with the anesthetic more quickly than do other tissues of the body, because the rate of blood flow through an organ bears a direct relation to the speed of saturation (Haggard, 1924). The fat depots of the body are the last to reach anesthetic equilibrium because of their poor blood supply, and adipose tissue may contain little anesthetic at the time when the concentration in the brain is such that surgical anesthesia has already occurred. Under these circumstances a second diffusion gradient is established between the brain and other tissues. During short operations with the rapidly acting anesthetics, when anesthesia is discontinued there are thus two gradients along which the brain loses the anesthetic—one extending to the lungs and the other to the tissues. The various organs and tissues of the body may be viewed as a huge buffer system which acts to retard the induction of anesthesia, to hasten elimination of the anesthetic from the brain (under such a special circumstance as mentioned above) and to retard its final elimination from the body (Haggard, 1924). On the other hand, the buffer system serves to retard emergence from anesthesia which has been maintained sufficiently long so that the buffer tissues are saturated.

Concentrations of Ether and Chloroform in the Blood and Inspired Air. The clinical data available on the concentration of anesthetic in the blood and inspired air during different depths of anesthesia are still not complete. Most of the information has been obtained from experiments on animals, and some of the discrepancies reported arise from the difficulties in judging depth of anesthesia. Another factor of importance is the source of blood on which determinations are made. For example, during induction, the concentration of anesthetic in the venous blood coming directly from an organ is the only index to the degree of saturation. The following figures should therefore be taken as approximations which are serviceable chiefly for comparing ether and chloroform.

Ether. Induction of anesthesia requires a concentration of ether vapor in the inspired air of from five to seven volumes per cent. This amounts to from 15 to 21 mgm of ether in every 100 cc of air. As the desired plane in stage III is reached, the concentration is gradually reduced to four or five volumes per cent. The anesthetist naturally does not stop to analyze the concentration of ether under the mask but depends upon the rate of ether administration and the response obtained to guide him. If the inhalation of five or six volumes per cent of ether is continued sufficiently long, respiratory failure ultimately ensues. Higher concentrations (10 to 11 volumes per cent) cause death more rapidly. The concentration of ether in the blood at the time of respiratory arrest is about 150 to 170 mgm per cent. The blood levels for the different planes of stage III are approximately as follows: plane i, 110 mgm per cent; plane ii, 120 mgm per cent; plane iii, 130 mgm per cent; plane iv, 140 mgm per cent.

Chloroform. Anesthesia with chloroform is accomplished with much lower concentrations of this agent in the blood and inspired air than are needed with ether. Surgical anesthesia can be obtained with 1.5 volumes per cent (7.5 mgm per cent) in the inhaled air. This is one-third that required for ether. The breathing of two volumes per cent of chloroform for any extended period proves fatal. The blood concentration at death is between 40 and 60 mgm per cent. Inasmuch as the difference between the anesthetic and fatal concentrations of chloroform in the air is only 0.5 per cent, the margin of safety in this regard is narrow. When one also considers the time factor imposed on chloroform anesthesia by the fall in blood pressure and the danger of liver damage, the great superiority of ether over chloroform is at once evident.

The concentrations of ether and chloroform in the blood and inhaled air necessary for different levels of anesthesia are indicated in Table 1 (Buckmaster and Gardner, 1907; Haggard, 1924; Robbins, 1935, 1936).

Table 1

CONCENTRATIONS OF ETHER AND CHLOROFORM IN THE BLOOD AND INHALED AIR

CONCENTRATION IN BLOOD

	Chloroform mgm %	Ether mgm %
Light anesthesia	25–30	100–110
Deep anesthesia	30–40	130–140
Respiratory failure	40–70	160–170

CONCENTRATION IN INHALED AIR

	Chloroform volumes %	Ether volumes %
Not sufficient for anesthesia	0.5–0.7	1.5–2.5
Light anesthesia producible after prolonged inhalation	1.0	3.0–3.5
For maintenance of surgical anesthesia	1.5	4.0
Respiratory arrest	2.0	7.0–10.0

Contraindications. *Ether* is naturally to be avoided when general anesthesia as such is contraindicated. In acute respiratory infections and in chronic pulmonary diseases such as tuberculosis, bronchiectasis, etc., ether is not desirable due to the bronchopulmonary irritation and stimulation of secretion which it causes. It is also best not employed in patients with advanced renal disease. Where an open flame or actual cautery is in use, ether is dangerous unless special precautions are observed.

Chloroform, although it has the advantages over ether of affording more rapid induction, less excitement and pulmonary irritation, less postoperative nausea and vomiting, and greater muscular relaxation, possesses no indispensable advantages which can offset the dangers incident to its use. It has been estimated that ether causes one death in 16,000 anesthesias, whereas deaths from chloroform occur nearly five times as frequently. Chloroform is particularly contraindicated in patients with hepatic, cardiac and renal disease, and also in those with anemia, acidosis, or diabetes. Chloroform is still used in the tropics where ether is often difficult to administer by the open drop method because of its high volatility.

Tolerance and Idiosyncrasy. It is generally stated that there is a cross-tolerance between alcohol and the methane series of anesthetics. This is particularly manifest during the induction period. It is common knowledge, for example, that addicts to alcohol are hard to anesthetize, but this is less difficult with chloroform than with ether. Morphine addicts are also said to be relatively insusceptible to the anesthetic action of ether. Patients with hyperthyroidism often react badly unless proper preanesthetic medication has been given. Contrary to general opinion, fat people do not require more anesthetic than non-obese persons of equal weight. Despite the affinity of ether and chloroform for lipids, little anesthetic agent reaches fat depots due to their poor blood supply.

Explosiveness. Chloroform is not inflammable. Inasmuch as ether is the anesthetic most frequently used, many explosions and fires have occurred because of it. The accidents are not serious as a rule when the open method of ether administration is used. Ether vapor is more than twice as heavy as air and is carried downward to the floor of the operating room. If an open flame is absolutely necessary during the use of ether by the open method, it should be placed at least 18 inches above and the same distance to the side of the ether mask. The closed method is safer if an open flame cannot be avoided. The introduction of the closed method, however, has made ether explosions much more serious because of the employment of oxygen which promotes the rapid propagation of ether flames and violent detonation. Mixtures of nitrous oxide and ether are practically as dangerous as those of oxygen and ether. If the flames reach the lungs of the patient, the tissue may be so burned that death ensues, or the explosion may rupture the lungs. The cautery should not be used about the head or neck of a patient under ether anesthesia. It is permissible on other parts of the body only if the Trendelenburg position is employed (so that the cautery is higher than the ether), provided the usual screen is in place and all air currents are avoided.

When ether anesthesia is discontinued at the end of an operation, the exhaled air of the patient is probably still inflammable for from 10 to 15 minutes. During prolonged ether anesthesia, the body cavities and tissues contain explosive concentrations of the chemical. For example, the use of the cautery on fatty tissue may cause a local flame. Anesthetic gases may also find their way into the air bubble of the instrumented bladder and explode when ignited by the spark of a fulguration apparatus.

Miscellaneous Uses of Ether

Ether has been employed as a *local anesthetic* on the skin in the form of a spray, in the same manner as ethyl chloride. Ether, if rubbed on the skin, produces a *rubefacient action* similar to that of alcohol or chloroform. It is less irritant than chloroform, however, because it evaporates more quickly. Occasionally, ether is used in superficial wounds as an *antiseptic* and *cleansing solvent*. Ether has been given in small doses orally as a *stomachic* and *carminative,* in the form of *Spirits of Ether* (*Hoffmann's Drops*), N.F., or *Compound Spirit of Ether* (*Hoffmann's Anodyne*), N.F. The dose of either is four cc. Ether is sometimes used as an *expectorant* in cough medicines. A final use of ether is for its *"stimulant" action* in cases of fainting or collapse. For this purpose, it may be combined with aromatic spirits of ammonia or injected subcutaneously in one cc quantities. Any action that ether may exert under these circumstances is purely one of reflex sensory stimulation. The administration of ether in olive oil or caoutchouc (latex) by rectum, as used by some for obstetrical analgesia, is also of value in some cases of *status asthmaticus* which have become refractory to all ordinary therapeutic measures, including epinephrine.

Miscellaneous Uses of Chloroform

Chloroform is employed as a *rubefacient* or *counterirritant* in liniments, such as *Chloroform Liniment,* U.S.P. *Chloroform Water,* U.S.P., B.P., is sometimes prescribed orally in four cc doses as a *carminative*. This preparation is also used as a *vehicle* for cough medicines and sedatives.

For the production of *obstetrical analgesia* chloroform is still used in deliveries performed in the home or in out-of-the-way communities where skilled assistance is not available. Relief of pain is obtained by the inhalation of two cc (one-half teaspoonful) of chloroform poured on cotton or blotting paper which is then placed in the bottom of a drinking glass held in the patient's hand. Effective analgesia is obtained by a very few inhalations. No opportunity for complete anesthesia exists because as soon as stage II appears consciousness and muscular coordination cease. The hand drops, automatically ending the administration. As consciousness clears and pain returns, the patient resumes the inhalation. Analgesia may last for 20 minutes or more after one such treatment. The method is said to be relatively safe and has also been used for relief during the changing of painful dressings. The danger of entering the delirium stage and of precipitating ventricular fibrillation appears too great to recommend the use of this form of inhalation anesthesia.

DIVINYL ETHER

Historical. Divinyl ether is also called *vinyl ether, vinethene* and *divinyl oxide.* It was introduced as an anesthetic at the suggestion of Leake and Chen (1930) who believed that this compound might combine the potency of diethyl ether with the rapidity of induction and low toxicity of ethylene. Ruigh and Major (1931) subsequently synthesized the first pure divinyl ether. Pharmacological studies of its properties soon followed (Leake and associates, 1933; Goldschmidt and coworkers, 1934), and numerous clinical reports have appeared concerning its use for surgical anesthesia.

Chemistry and Preparations. Divinyl ether has the following structural formula: $CH_2=CH-O-CH=CH_2$. The commercially available preparation is *Vinethene* (N.N.R.). This is a clear, colorless fluid possessing a slight ethereal odor and a faint purplish fluorescence. It is very volatile, more so than ether, and boils at 28 to 31 C. Divinyl ether is approximately as inflammable and explosive as ethyl ether.

Divinyl ether undergoes decomposition on exposure to light or air, or to minute amounts of strong acids. It is marketed in dark bottles and should be kept tightly stoppered in a cool place, and must never be used more than 24 hours after the bottle has first been opened. Chemically pure divinyl ether is so volatile that if used as such it is likely to cause moisture to freeze on the anesthetic mask or in the gas machine. To overcome both this disadvantage and that of rapid deterioration, vinethene contains 3.5 per cent absolute alcohol and 0.01 per cent of a non-volatile oxidation inhibitor, phenyl-alpha-naphthylamine.

Anesthetic Actions. Divinyl ether possesses the characteristic actions on the central nervous system of the methane series of anesthetics. Its high potency and rapidity of action, however, make it unique. Divinyl ether has an anesthetic power of 100 per cent in that it can produce Stage IV anesthesia without preliminary medication or asphyxia (Figure 4). Goldschmidt and coworkers (1934) estimate its relative anesthetic potency as compared to ethyl ether to be 7:1, and also conclude from animal experimentation that divinyl ether has a wider margin of safety. This fact is of little or no advantage in clinical anesthesia because divinyl ether is so potent and produces deep anesthesia so rapidly that a dangerous or lethal plane may easily be entered. Thus the hazard accompanying its use is actually greater than that with ethyl ether.

Anesthetic Concentrations. In man, surgical anesthesia with good abdominal relaxation requires 18 mgm per cent of divinyl ether in the blood, only one-seventh of the concentration necessary for ethyl ether. For extra-abdominal operations in which marked muscular relaxation is unnecessary, a blood level of 11 mgm per cent is sufficient. The lethal concentration in man is not known. In the dog, a species requiring 28 mgm per cent in the blood for full surgical anesthesia, the lethal concentration is 68 mgm per cent.

Induction. Induction of anesthesia with divinyl ether is smoother and more rapid than that obtainable with ether, chloroform, or nitrous oxide. Unconsciousness occurs in one-half minute to one and one-half minutes and muscular relaxation sufficient for laparotomy is obtained in two and one-half minutes. The incidence of excitement is low, less than 0.5 per cent, and no struggle is seen. So rapidly does induction occur that analgesia without unconsciousness is rarely observed. No laryngeal irritation or spasm complicates induction and the masseters usually relax promptly so that an airway may be inserted with ease.

Surgical Anesthesia. Surgical anesthesia occurs rapidly, two or three times as quickly as with ethyl ether. It is evenly maintained provided the anesthetist has had experience with divinyl ether and watches the patient closely. It must be re-emphasized that it is easy to pass from the level of surgical anesthesia to Stage IV with divinyl ether anesthesia. Under no circumstances, therefore, should the anesthetic be pushed.

The *physical signs* under anesthesia with divinyl ether differ somewhat from those observed with other inhalation anesthetics. The characteristic signs during induction and plane i can be recognized only with difficulty because of the rapidity of action. During surgical anesthesia, the respirations are more rapid and somewhat more shallow than normal. If an adequate airway is maintained, the color remains good. The eye movements do not cease as rapidly as with other anesthetics. Thus the abdominal musculature may be sufficiently relaxed for surgical procedures and yet the eyelids and eyeballs may still be moving as in lighter planes of anesthesia. Depth of anesthesia must be judged chiefly by the rate, amplitude and character of the respiration.

Blood Pressure and Respiration. The blood pressure may undergo a slight and transitory fall but soon returns to normal and remains there throughout the period of anesthesia. Divinyl ether has no deleterious effect on the cardiovascular system. The respiratory rate may be somewhat elevated. Lethal concentrations cause respiratory depression and arrest before cardiac failure takes place.

Muscular Relaxation. Muscular relaxation is approximately as complete with divinyl ether as with ethyl ether, and therefore sufficient for all general surgical purposes. Some surgeons claim that muscular relaxation is as complete as with chloroform. Uterine activity during labor is not inhibited by divinyl ether used for obstetrical analgesia (Bourne, 1935).

Salivation. Divinyl ether is less irritant to the respiratory passages than is ethyl ether, but causes an increase in salivation, due perhaps to chlorinated ether impurities, decomposition products, or the material which is added to inhibit oxidation. After atropine, salivation is considerably reduced, and any excessive secretion which occurs can be controlled by a second dose of atropine.

Recovery and Postanesthetic Period. Recovery from anesthesia is rapid, smooth and without excitement. When anesthesia lasts only one-half hour, complete recovery occurs in less than four minutes. The incidence of vomiting is exceptionally low, being less than two per cent. Respiratory complications are rare and divinyl ether apparently causes few postoperative pulmonary sequelae.

Vital Organs. The heart is unaffected by divinyl ether, which can thus be used in patients with cardiac disease. There is also freedom from renal irritation. The gastro-intestinal musculature is not markedly inhibited nor is uterine activity depressed.

The possible effects of divinyl ether on the *liver* represent the most serious toxic potentiality. It seems that postanesthetic central lobular necrosis of the liver similar to that caused by chloroform occasionally occurs, and in a study of several fatalities after divinyl ether, liver changes were noted in at least two cases. In a series of 2675 divinyl ether anesthesias (Ravdin and associates, 1937), three deaths occurred but these were in no manner related to the anesthesia or to any postanesthetic liver damage. In each of the few reported cases of damage to the liver, when the anesthetic could reasonably be blamed, there is evidence either of prolonged use of divinyl ether, excessive dosage, or coincidental anoxia. If these three factors are strictly avoided, there appears to be no danger of damage to the normal liver. Animal experiments show that divinyl ether is much less toxic than chloroform for the liver. In order to produce hepatic injury, divinyl ether must be given not only for a long period but also there must be an associated anoxia (Goldschmidt and associates, 1934, 1937). In addition to the prevention of anoxia by maintenance of a patent airway and an adequate concentration of oxygen at all times, it is also important that, if possible, a high carbohydrate, high protein and low fat diet be given prior to anesthesia (page 66). Obviously, patients known to have liver disease should not be anesthetized with divinyl ether. Cyanosis should be avoided and its appearance is a signal for the administration of oxygen and a change of anesthetics.

Methods of Administration. Divinyl ether may be given by the open drop method, the semi-open technic, or with any of the usual gas machines. For short operations, lasting not over one-half hour, the open drop method is employed and preferred. Either an open face mask or the simpler technic of fluffing several thicknesses of gauze and applying the latter directly to the nose is employed. Divinyl ether is dropped on the mask or gauze at the rate of 60 to 80 drops per minute for adults and older children, half this rate sufficing for infants. Too high a concentration of vapor should be avoided and an adequate airway should be maintained. If difficulty is experienced in obtaining or maintaining sufficiently deep anesthesia with the open method, a wet towel may be wrapped around the base of the mask or gauze in order to decrease dilution by air.

For operations lasting over one-half hour, a gas machine is employed, and divinyl ether is volatilized with pure oxygen. Not only is the anesthetic agent conserved, but of greater importance is the fact that an abundance of oxygen is assured. For operations lasting much longer than one hour, divinyl ether should not be used. If the operation lasts longer than contemplated and extends over the one and one-half hour limit of safety at present adopted for divinyl ether, another anesthetic agent should be substituted.

Advantages. Divinyl ether provides a pleasant and rapid induction and recovery. It produces the same degree of muscular relaxation obtainable with ethyl ether, but accomplishes this much more quickly and without the excitement, prolonged recovery, pulmonary irritation, postoperative vomiting and other objectionable features common to ethyl ether. Except for the slight possibility of liver damage already discussed, divinyl ether causes no untoward changes in the vital organs or metabolic functions of the body.

For operations of short duration when rapid induction and recovery must be combined with complete muscular relaxation, divinyl ether occupies a definite sphere of usefulness. It does not entail the anoxia of nitrous oxide anesthesia and gives much greater relaxation. Furthermore, it requires no cumbersome apparatus for short operations, and can thus be used in the ward and home or for ambulatory patients in the physician's office. Divinyl ether may also serve as an induction anesthetic for other agents, or to supplement nitrous oxide or ethylene anesthesia when additional muscular relaxation is needed. It has also been employed in combination with ethyl ether, the two fluids being mixed in the ratio of one part of divinyl ether to three parts of ethyl ether.

Indications and Special Uses. The advantages of divinyl ether enumerated indicate its usefulness especially for short operations when greater muscular relaxation is needed than is obtainable with the anesthetic gases, when speedier induction and recovery are required than is allowed by ether, or when no special apparatus is available. It has been employed under these conditions in a wide variety of major surgical procedures, either alone or as a supplement to nitrous oxide or ethylene.

In *dental surgery* and *exodontia*, divinyl ether has distinct advantages over nitrous oxide. It is more rapid than nitrous oxide both in induction and recovery, avoids anoxia, requires no gas machine, and provides a longer period for operation and more complete relaxation. While more experience will be needed to determine the status of divinyl ether in dentistry, there can be no doubt that in many cases it may prove helpful. In *ophthalmology* and in *ear, nose and throat surgery*, divinyl ether may be employed in a variety of operations, and also where local anesthesia may need re-enforcement. Examinations of the fundi and myringotomies in children, for example, can easily be performed under divinyl ether anesthesia. In *orthopedic surgery*, the agent can be employed for anethesia for the fluoroscopic reduction of fractures, and the manipulation of bones and joints where repeated anesthetizations may be needed. In traumatic cases without surgical preparation, divinyl ether is useful. For *changing painful dressings*, especially in children, a few drops of divinyl ether are extremely helpful and may improve the morale of the entire ward. Only gauze and the bottle of anesthetic need be taken into the room. *Induction of general anesthesia* is done routinely with divinyl ether in some clinics. It is more rapid and smooth for this purpose than nitrous oxide and the excitement period is practically eliminated. If *spinal anesthesia* begins to wear off before the operation is completed, divinyl ether may be used. In *obstetrical procedures* divinyl ether may be employed for short operations. It gives sufficient muscular relaxation for perineal and deep pelvic surgery. It cannot be used for obstetrical analgesia because it acts too rapidly and causes deeper anesthesia than is desirable.

Disadvantages, Contraindications and Precautions. The chief disadvantage of divinyl ether is that it is not safely used for operations lasting much over one hour. Salivation is more frequent, even after atropine, than with other anesthetics. The slight possibility of liver damage requires attention to the liver function and diet before lengthy operations, and special care is necessary to avoid anoxia and cyanosis during anesthesia. Divinyl ether is contraindicated in patients with liver disease or hepatic insufficiency. In patients with bronchopulmonary disease in whom the possibility of excess mucus or salivary secretion might be undesirable, divinyl ether should be used with caution. The drug should not be given to those in whom oxygen want may develop easily. Due to its extreme volatility, the use of divinyl ether at high altitudes may offer difficulties.

Precautions to be observed are never to "push" the anesthetic, to maintain sufficient oxygenation, to limit the time of use by the open method to one-half hour and by the closed method to one and one-half hours, and to observe the same care against fire and explosion hazards as is observed with ethyl ether. Above all, divinyl ether should be used only by those thoroughly familiar with its anesthetic properties and limitations. Divinyl ether is a new anesthetic, and its toxicity and exact position cannot yet be fully defined.

ETHYL CHLORIDE

Historical. Ethyl chloride was introduced into medicine as a local anesthetic. For centuries it was known that limbs long in contact with snow or ice became insensitive. James Arnott in 1849 first used cold routinely for anesthesia by applying an ice and salt mixture to the skin. Ten years later, Richet used the evaporation of ether from the skin for producing anesthesia. Ethyl chloride soon replaced ether because of its lower boiling point. Flourens (1847) was the first one to call attention to the general anesthetic properties of ethyl chloride. This observation was overlooked, however, until 1894 when a Swedish dentist, Carlson, while applying ethyl chloride to a patient's gums, noted that the patient fell asleep and that the teeth could be extracted without pain. Undoubtedly the vapor was inhaled. Ethyl chloride was then reintroduced into general anesthesia.

Chemistry. *Ethyl Chloride* (*Monochlorethane*), U.S.P. B.P., C_2H_5Cl, is a very inflammable, colorless and highly volatile fluid. Its boiling point is 12 to 13 C. The vapor has a peculiar ethereal odor and is sharp and sweet to the taste. Ethyl chloride is slightly soluble in water, less so in the blood, and readily dissolves in alcohol or ether. It is dispensed in special glass or metal tubes as a liquid under pressure for use in local anesthesia. The tubes have a pin-hole exit covered by a spring cap, which when opened allows the fluid to issue forth as a fine spray with some force. The tubes should be stored in a cool place.

Use as a Local Anesthetic. Ethyl chloride freezes tissues when it is used as a fine spray and allowed to evaporate from the skin. The tissues reach a temperature of −20 C. The tube is held about 12 inches from the skin and the spray is directed against the site for operation, the warmth of the hand causing the fluid to volatilize and be ejected from the tube. The tissues become white and frozen and the adjacent skin should be prepared with vaseline to insure against sloughing.

Disadvantages. Ethyl chloride has a limited field of usefulness as a local anesthetic. The process of thawing is painful. Dissection of frozen tissue is difficult. Furthermore, freezing injures cells, lowers resistance to infection, and delays healing. Finally, anesthesia rarely lasts more than from a few seconds to a minute, and if the operation requires a longer time than was anticipated, obvious difficulties ensue. Consequently ethyl chloride can be used only for such minor purposes as the incision of boils, whitlows, removal of splinters, etc. Its main value is a psychic one, to distract the patient so that a simple incision, which ordinarily would not require local anesthesia, can be made.

Use as a General Anesthetic. Ethyl chloride produces the characteristic actions of the methane series of anesthetics. The presence of chlorine probably contributes to its rapid and intense action, but renders the drug more dangerous than non-halogenated congeners.

Induction and Recovery. General anesthesia produced by ethyl chloride appears and disappears rapidly. Induction requires only one-half minute to one and one-half minutes, and recovery occurs in a few minutes after administration of the anesthetic ceases. Excitement and struggle are usually absent due to the rapid induction. The chemical is relatively non-irritating to mucous membranes of the respiratory tract and causes no sense of suffocation as does ether. After-effects are mild.

Anesthetic Concentrations. Surgical anesthesia can be maintained by inhaling slightly over two volumes per cent of ethyl chloride vapor. The blood concentrations of ethyl chloride necessary for surgical anesthesia in man are as follows: 20 mgm per cent for light anesthesia; 30 to 150 mgm per cent for deep anesthesia; 40 to 180 mgm per cent for respiratory arrest. It is obvious from these data that there exists a considerable overlap of anesthetic, toxic, and lethal concentrations.

Technic of Administration. In order to produce surgical anesthesia, ethyl chloride must be present in the inhaled air during induction in a concentration of four to five volumes per cent. This can be accomplished only by the use of a mask. Ethyl chloride can be sprayed on the mask, a wasteful procedure, or it can be used in smaller amounts as a fluid poured onto a semi-closed mask. By the use of a gas machine, ethyl chloride can be volatilized and employed as a gas.

Disadvantages and Dangers. Ethyl chloride is a halogen-containing hydrocarbon with the potentiality for damaging parenchymatous organs. Induction and recovery are so rapid that the danger signals are indefinite and even a trained anesthetist has difficulty in maintaining an even anesthesia. Muscular relaxation is incomplete at safe depths of anesthesia. Although ethyl chloride is less toxic than chloroform, ventricular fibrillation and sudden cardiac arrest may occur (Guedel and Knoefel, 1936).

TRICHLOROETHYLENE

Trichloroethylene (N.N.R.) is a rather pungent, sweet-smelling, clear, colorless, and volatile liquid, having the formula $CHCl{:}CCl_2$. It has been used for general anesthesia (Jackson, 1934) and although its principal actions are similar to those of other members of the methane series of anesthetics, it has no advantage or indication as a surgical anesthetic (Report of the Council, 1936).

Therapeutic Uses. Trichloroethylene is used as a solvent in industry where it has produced poisoning. During the World War of 1914–1918, it was noted by Plessner (1915) that some workers using trichloroethylene in the airplane industry developed a peculiar bilateral loss of sensation over the distribution of the fifth cranial nerve. Oppenheim suggested to Plessner that he use the drug therapeutically in *trigeminal neuralgia* for the relief of the severe paroxysms of pain characterizing this disease, and a number of patients so treated were benefited. Trichloroethylene is available in one cc sealed frangible glass tubes. The tube is broken, placed in the bottom of a tumbler and the vapor is inhaled until the odor disappears. A second tube may be used if incomplete relief is obtained from the first. This treatment of patients with trigeminal neuralgia may be repeated three or four times daily for several weeks. The results obtained have been reviewed by Glaser (1931) who reported 15 cases of his own and 177 in the literature. Complete relief was obtained in about 15 per cent of cases and partial relief in from 13 to 75 per cent. The attacks diminish both in severity and frequency. A later report by Horrax and Poppen (1935) on 90 cases of tic douloureux treated with trichloroethylene indicates that about one-half of the patients received sufficient benefit to allow postponement of surgical procedures for at least six months. The remaining patients were not relieved.

The *mechanism of action* of trichloroethylene in trifacial neuralgia is obscure. The facial anesthesia, which was first noted in industry and which led to the therapeutic use of the chemical, is not evident when trichloroethylene is employed clinically. It is possible that an impurity accounted for the anesthesia. The drug has no marked effect on neuralgias other than the trigeminal type, unless it be that of the glossopharyngeal type. Nevertheless, it is likely that the relief obtained is due to the central depressant actions of the drug, the inhalation of the prescribed amount of which may produce stage I anesthesia (Rubinstein and coworkers, 1939). Giddiness, sleepiness and even transient unconsciousness have been observed. Lassitude, nausea, and palpitation are also occasionally noted. The permanency of relief obtained by some individuals without continued use of the drug is unexplained. The disease, however, is likely to exhibit spontaneous remissions. Although, as a rule, no serious consequences occur from the inhalation of trichloroethylene, there is danger of overdosage from self-medication. Eichert (1936) reports two cases which developed *toxic psychoses,* with temporary but alarming symptoms.

Trichloroethylene has been used for the relief of pain in *angina pectoris.* Love (1937) reports that the inhalation of one cc, three or four times a day, may prove moderately helpful in some patients, and believes that the central sedative and hypalgesic action is the basis for this. Krantz and coworkers (1935) have investigated the pharmacological actions of the drug on blood vessels. It would seem doubtful that any direct action on the coronary circulation can account for the relief of anginal pain which may sometimes occur. Rubinstein (1937) obtained relief of *migraine* from inhalation of trichloroethylene in all of his small series of six patients. Less success was observed in this respect by Geiger and Goodman (1937) who found that only about 20 per cent of patients with headache, whether migrainous or otherwise, obtain definite relief from trichloroethylene, but this was sometimes dramatic. It is believed that the central depressant action operates here as it does in the relief of trigeminal neuralgia.

The *toxicology* of trichloroethylene as used in *industry* has been reviewed by Hamilton (1934). She records a series of 284 cases in which 26 deaths occurred. The therapeutic use of the drug carries with it no such danger and it is likely that industrial poisoning may be complicated by the presence of toxic impurities. Damage to the liver is not observed when trichloroethylene is used industrially or clinically, and the drug is less dangerous than chloroform. Despite the fact that no serious untoward effects have been reported from the proper use of this chemical in the relief of certain forms of pain, it should be employed cautiously by patients with the knowledge and supervision of the physician.

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CHAPTER 6

GENERAL ANESTHETICS

II. NITROUS OXIDE, ETHYLENE, CYCLOPROPANE, ACETYLENE

NITROUS OXIDE

History. Nitrous oxide (nitrogen monoxide, protoxide, "laughing gas") is the oldest of the inhalation anesthetics, and was prepared by Priestley in 1776. In 1799, Sir Humphry Davy, after experiments on himself, announced that nitrous oxide had anesthetic properties and suggested that it be used to allay physical pain in surgical operations. He wrote as follows, "As nitrous oxide in its extensive operation appears capable of destroying physical pain, it may probably be used with advantage during surgical operations in which no great effusion of blood takes place." Davy's suggestion passed unheeded, however, until many years later. It is said that a surgeon named Elsworth, in January 1843, amputated a leg under nitrous oxide anesthesia. The manner in which Wells, in 1844, became interested in nitrous oxide through Colton's demonstration has been described. In 1868, Andrews in Chicago introduced oxygen administration with nitrous oxide, the manner of its use today, and in 1880 Bert introduced the use of nitrous oxide-oxygen mixtures under pressure. As a result of Bert's investigations, the first accurate knowledge of the action of nitrous oxide became known.

Chemistry, Preparations and Properties. Nitrous oxide, N_2O, while not an organic compound, has the typical action of the methane anesthetic series. It is the only inorganic gas which is serviceable as an anesthetic agent. There are several oxides of nitrogen, some being quite toxic, especially the higher oxides such as nitric oxide which may be present in nitrous oxide as an impurity. *Nitrous Oxide* (*Nitrogen Monoxide,* U.S.P., B.P.), is a colorless gas which has a slight but characteristic odor and somewhat sweetish taste. It is marketed in steel cylinders as a colorless liquid under a pressure of 30 atmospheres. As the pressure is released, nitrous oxide returns to the gaseous state. It is readily soluble in water and is heavier than air.

Nitrous oxide is very soluble in blood which takes up 45 volumes per cent, if exposed for a sufficiently long period to high concentrations of the gas. Nitrous oxide does not combine with hemoglobin, and is carried in the blood in solution only. It is excreted unchanged through the lungs but a small fraction, due to the rapid diffusion of the gas, escapes through the skin. The chemical affinities of the gas are feeble and this fact probably accounts for the freedom from side-actions in its use.

The oxygen in nitrous oxide is unavailable for animal respiration, because nitrous oxide does not decompose in the body. Seeds cannot germinate or plants grow in nitrous oxide. A glowing splinter, however, bursts into flame if thrust into the gas, exactly as if thrust into oxygen. On the other hand, the sulfur flame which burns with little heat is extinguished. Thus, only at high temperatures is oxygen dissociated from nitrous oxide. Although nitrous oxide is not inflammable, it supports combustion as actively as does oxygen when it is present in proper concentration with an inflammable anesthetic. Fatal explosions have occurred with ether-nitrous oxide mixtures. Nitrous oxide also enhances the explosiveness of ethylene, and the induction of ethylene anesthesia with this gas entails a definite element of danger. The violence of an ethylene-nitrous oxide explosion is greater than that of ethylene mixed with either oxygen or air. If the two gases are used together, the tanks should not be opened at the same time. In the presence of oil, mixtures of oxygen and nitrous oxide at high pressures are also explosive.

Anesthetic Action

Inhalation of Undiluted Nitrous Oxide. The inhalation of undiluted nitrous oxide produces rapid but light anesthesia. So rapid is the induction that the stages of anesthesia are difficult to follow. When the full effect of the gas is manifested, the patient is barely in plane i of stage III. Nitrous oxide alone, therefore, is not a powerful anesthetic. Undiluted nitrous oxide is employed for very short operations, as in dentistry, and is administered by the use of a tight-fitting mask to exclude air. Dental anesthesia with nitrous oxide is preferably performed with five per cent to 10 per cent oxygen mixtures. No special preparation is needed for these short procedures except a preliminary fast of several hours. The patient may sit in a chair and his clothing need not be removed.

The course of anesthesia with undiluted nitrous oxide is as follows:

Preliminary Effects. The patient notes a sweetish taste. There is no sense of suffocation, despite the absence of air, because nitrous oxide is nonirritating and induction of anesthesia is rapid. Numbness and a sense of comfortable warmth are experienced and noises or rushing sounds are heard in the ears. Confusion rapidly intervenes, and occasionally the patient exhibits exhilaration or bursts into laughter. The respiration becomes deeper and fuller, and the pulse is bounding. Consciousness is lost within 20 to 30 seconds.

Second Stage Anesthesia. The patient may experience extremely vivid dreams, amounting in fact to hallucinations. Many women, for example, have claimed that they were sexually assaulted by the dentist while under nitrous oxide, and insist upon this despite the fact that their husbands may have been with them throughout the operation. Several famous medicolegal cases are based on the property of nitrous oxide to produce hallucinations. The doctor or dentist, therefore, should always have an assistant, preferably a female nurse, when using the gas on women. The course of anesthesia is too rapid to allow for much excitement or struggle. The respirations are deep and rapid, the pulse is accelerated and the blood pressure elevated. The pupils are dilated, and the skin is dusky or cyanotic. Salivation and bronchial secretions are not stimulated. This stage lasts from one-half minute to one and one-half minutes.

Surgical Anesthesia. From one to two minutes after the anesthetic is started, plane i of stage III is entered. The limbs are flaccid, the pupils are still dilated, and the face is cyanotic. Respirations are slightly irregular and stertorous due to relaxation of the soft palate. The blood pressure may rise markedly because of increasing asphyxia. This rise may be due in part to the operative procedure because it is often absent in normal subjects not undergoing surgery. Wright and Thompson (1930) studied the blood pressure responses of healthy persons during the inhalation of pure nitrous oxide and found that after a preliminary rise (psychic) there usually occurred a gradual or sharp decline in blood pressure due to the depressant effect of anoxia on the ventricular myocardium. Electrocardiographic changes occur, chiefly in the T wave in lead two, and are similar to those seen in anoxia, namely, reduction, inversion or abolition of the T wave (Ward and Wright, 1929). The medullary centers are not depressed because of the innocuousness of nitrous oxide. The accompanying anoxia actually stimulates the respiratory and vasomotor centers. Nitrous oxide and ethylene, in fact, are respiratory stimulants throughout anesthesia, and never produce depression by their own action.

When the respirations become stertorous or noisy and the face cyanotic, the gas is discontinued and the mask removed. The operation is now performed. Anesthesia lasts for about thirty seconds to one minute after the mask is lifted, and the operative period is thus very short. The patient is fully awake after one to three minutes. The time from start to finish is only three to five minutes. Anesthesia can be continued longer if some air is let into the mask periodically to overcome the asphyxia, but this is likely to result in an irregular and difficult anesthesia.

Asphyxial Stage. If the administration of undiluted nitrous oxide is continued beyond the stage of anesthesia just described, asphyxial signs rapidly appear. Intense blue-black cyanosis is present, the blood pressure may be markedly elevated, due to the asphyxia, and the pulse is slow. The corneal reflex is absent and muscle twitchings appear and proceed to tonic muscular spasms. Respirations, which are violent as severe asphyxia develops, soon become shallow and irregular, and in two to four minutes cease entirely. The heart continues to beat for some time and therefore restorative measures are fairly easy. The respiratory and circulatory changes are almost entirely secondary to asphyxia.

It should be emphasized that *cyanosis is never an accurate guide to the degree of anoxemia.* A cyanotic color depends on the amount of reduced hemoglobin in the blood, and a patient with severe anemia may be in fatal oxygen lack and yet not have the five grams per cent of reduced hemoglobin necessary for the exhibition of cyanosis. An individual with a hemoglobin value of less than 40 per cent cannot be depended upon to develop cyanosis. The moderately anemic patient with a hemoglobin value of 60 per cent may show cyanosis late in the course of anoxemia, when half of the hemoglobin has already been reduced. Conversely, the polycythemic person may normally be somewhat blue, or become blue very early in the course of nitrous oxide anesthesia when there is still an adequate amount of oxyhemoglobin in the blood. In addition, factors such as the thickness and color of the skin, the density of its capillary network, and the type of lighting used in the operating room all modify the appearance of cyanosis and hence reduce the value of this physical sign. In colored patients, it is difficult to detect cyanosis.

The *muscle twitchings,* especially of the limbs, seen in the asphyxial stage of anesthesia with nitrous oxide, are known as *jactitations.* Convulsions, so prominent in other forms of asphyxia, either do not occur under nitrous oxide or are mild because of the depressant action of the anesthetic on the motor cortex.

Recovery. Recovery is rapid, uneventful and generally without after-effects. Occasionally, slight headache or dizziness may be noted. Hyperglycemia and acidosis, if they develop, are due to anoxia. So rapidly is the gas eliminated from the body that it is no longer detectable in the blood five minutes after anesthesia has been terminated. Nitrous oxide is excreted unchanged, chiefly through the lungs. A small fraction is lost through the skin (Orcutt and Waters, 1933).

Contraindications. The contraindications to the use of undiluted nitrous oxide are in reality those to anoxia. The administration either of undiluted or high concentrations of nitrous oxide is contraindicated in a patient to whom asphyxia, even for relatively brief periods, would be harmful. This especially includes patients with cardiovascular disease, elderly persons, and hypertensive and hyperthyroid individuals. It is often impossible to anesthetize hysterical or highly excited patients with nitrous oxide, and addicts to alcohol may also offer difficulty. Very young children and persons with high metabolic rates are especially intolerant of oxygen deficiency and often cannot be anesthetized satisfactorily with nitrous oxide. For these reasons, even for very short periods of anesthesia, undiluted nitrous oxide is greatly inferior to a mixture of the gas and oxygen.

Inhalation of Mixtures of Nitrous Oxide and Oxygen. In order to allow longer periods of anesthesia than the two-minute limit imposed by asphyxia when undiluted nitrous oxide is used, air or oxygen must be combined with the gas. When a 90:10 mixture (90 volume per cent of nitrous oxide and 10 volumes per cent of oxygen) is inhaled, it is just possible to bring most patients into the first plane of stage III anesthesia (Figure 4), but early signs of anoxia may develop if inhalation of the mixture is continued for any length of time. When nitrous oxide is mixed with 20 volumes per cent oxygen, asphyxial signs are entirely missing. Anesthesia may now be continued, usually for long periods, although the reduced concentration of nitrous oxide weakens the anesthetic action. For example, most patients without preanesthetic medication do not enter the second stage of anesthesia from inhaling an 80:20 nitrous oxide-oxygen mixture. Exhilaration, laughter, staggering gait, slight drowsiness, moderate analgesia, and relatively normal touch sense are observed. Mental confusion occurs but loss of consciousness rarely results. When a sufficient amount of morphine and scopolamine or basal anesthesia with tribromethanol or barbiturate is given beforehand, an 80:20 mixture is quite capable of producing surgical anesthesia.

Under certain circumstances, adequate muscular relaxation can be obtained with nitrous oxide-oxygen mixtures by utilizing the technic described by McKesson (1920). Several minutes after anesthesia has been induced with nitrous oxide and oxygen, pure nitrous oxide is administered until the patient develops dilated pupils, muscular rigidity or spasm, and slow respiration. A single breath of pure oxygen is then allowed and anesthesia is continued with the original nitrous oxide-oxygen mixture. Complete muscular relaxation is obtained by this method and may last for the duration of the surgical procedure. The explanation of the phenomenon is not clear but its efficacy is well established. The patient must be healthy enough to withstand a short period of acute anoxia and the anesthetist should be an expert; otherwise, this procedure is not justified or safe.

Concentrations of nitrous oxide below 80 volumes per cent are capable of producing *analgesia*. The optimal concentration of the gas which allows analgesia without loss of consciousness or cooperation is from 35 to 40 volumes per cent (Seevers and associates, 1937).

The *physical signs* during surgical anesthesia with mixtures of nitrous oxide and oxygen naturally vary with the percentage of each gas and the character of the preanesthetic medication. For example, with a 90:10 mixture and preliminary morphine and atropine, the stage of surgical anesthesia is characterized by regular and stertorous respirations, a slightly dusky skin color without real cyanosis, a moderately elevated pulse rate and blood pressure, and moderately decreased tone. With a mixture of 80 volumes per cent nitrous oxide and 20 volumes per cent oxygen, the respiration, circulation and other vital processes are only slightly affected. Breathing may be slower and deeper without change in respiratory minute volume and the only detectable circulatory change is moderate dilatation of the peripheral capillaries.

Technic of Administration of Nitrous Oxide-oxygen Mixtures. Morphine combined with scopolamine or atropine is administered before nitrous oxide-oxygen anesthesia and greatly enhances the depth to which anesthesia may be carried (Figure 4). Preanesthetic sedation also allows more oxygen to be used in the gas mixture. Basal anesthesia with tribromethanol is frequently employed and nitrous oxide-oxygen is then given as the supplemental anesthetic.

A special gas apparatus and tight fitting mask are required. Anesthesia is induced with a 98:2 nitrous oxide-oxygen mixture, and as the patient enters plane i of stage III, the ratio is gradually changed to 90:10 or 85:15. The ratio of the gases can then be altered to meet the needs of the operation. If muscular relaxation is not complete, supplemental ether or cyclopropane may be administered. Muscle spasms due to insufficient oxygen should not be mistaken for emergence excitement or the anesthetist may erroneously give more nitrous oxide and increase the anoxemia. A difference of two or three per cent in the concentration of nitrous oxide often determines the success of the anesthesia.

Mechanism of Anesthetic Action. Nitrous oxide does not combine chemically with any constituent of the body, and tissues other than the central nervous system are quite unaffected by its presence. The question naturally arises as to whether nitrous oxide is purely an indifferent asphyxiant gas, like nitrogen or hydrogen, or whether it produces anesthesia by direct action on nerve cells. The former view prevailed for some time but it is now definitely known that nitrous oxide is an anesthetic and not an asphyxiant. Although the phenomena seen in anesthesia with pure undiluted nitrous oxide are partly asphyxial in origin, the evidence that nitrous oxide is an anesthetic is incontrovertible.

When nitrous oxide is administered with sufficient oxygen to prevent asphyxia, as in an 80:20 mixture, anesthesia may result in some patients. Indeed, consciousness may be lost with lower concentrations of nitrous oxide, and subanesthetic doses are definitely analgesic. This must be due to the action of the gas on the central nervous system; otherwise an 80:20 mixture would act as air does. For example, if nitrogen is substituted for the nitrous oxide in such a mixture, anesthesia ceases at once. Even if the oxygen content is reduced so that the mixture contains 90 volumes per cent of nitrogen and 10 volumes per cent of oxygen, no anesthesia occurs, whereas it is possible with most subjects to enter the first plane of anesthesia with a nitrous oxide-oxygen mixture of 90:10. Furthermore, respiratory arrest occurs earlier when undiluted nitrous oxide is breathed than when nitrogen is inhaled. Clearly, nitrous oxide is not acting solely through an asphyxial mechanism. Finally, frogs placed in pure nitrous oxide lose their reflexes in five and one-half minutes, but in pure hydrogen the reflexes are preserved for over an hour.

Rôle of the Asphyxial Factor. The asphyxial factor, although secondary, is usually essential for complete surgical anesthesia with nitrous oxide. Bert (1878, 1879) contended from his experiments on animals and patients that nitrous oxide was capable of producing complete anesthesia without asphyxia if given with oxygen under increased pressures. For example, he used an 85:15 mixture of nitrous oxide and oxygen under one and one-quarter atmospheres. This allowed for the administration of nitrous oxide under a pressure equivalent to that obtainable from the pure gas under atmospheric pressure and at the same time assured normal oxygenation of the blood. According to Bert this procedure resulted in adequate surgical anesthesia, and he concluded that if the partial pressure of nitrous oxide was raised to 760 mm of mercury, a sufficient quantity of the gas was dissolved in the blood to assure anesthesia regardless of the oxygen tension.

Brown, Lucas and Henderson (1927) have taken exception to the historical experiments of Bert. Duplicating his conditions on rabbits and cats, they were unable to produce anesthesia. Even when they administered an 80:20 mixture of nitrous oxide and oxygen under increased pressures extending at times to two atmospheres (partial pressure of nitrous oxide about 1200 mm of mercury), complete anesthesia was still not obtainable. The authors draw attention to the fact that criteria for adequate anesthesia are quite different today than they were in Bert's time, and conclude that anesthesia with nitrous oxide is only possible provided there is present a certain degree of anoxia.

It is possible, however, so to increase the partial pressure of nitrous oxide that death results in experimental animals in the absence of anoxia, but three atmospheres or more of pressure are needed (Bock, 1913; Lendle, 1929).

Margin of Safety and Accidents. The margin of safety with nitrous oxide is quite broad, more so than with any other anesthetic. The innocuousness of nitrous oxide in respect to the tissues and vital functions is demonstrated clearly by the fact that dogs, kept continuously anesthetized with nitrous oxide for three days, recovered as readily as if anesthetized for only a few minutes, and without any discernible ill effects. The blood concentrations of nitrous oxide at anesthetic and fatal levels offer no measure of the clinical safety of the gas. For example, the blood concentration of nitrous oxide during complete anesthesia with the undiluted gas is 50 mgm per cent, and at respiratory arrest it is 60 mgm per cent. The apparently narrow margin is due to the fact that the cause of death is asphyxia. If sufficient oxygen is present along with a blood level of 60 mgm per cent, no toxic effects are noted.

The safety of nitrous oxide is best indicated by the rarity of serious accidents and the extremely low mortality figures. With due consideration for the limitations of statistics on anesthetic mortalities, the figure quoted for nitrous oxide of one death in 5,000,000 administrations is probably of the correct order of magnitude. This indicates better results than for any other anesthetic.

Minor accidents due to excitement, temporary asphyxia or hallucinatory dreams may occur. A few cases of sudden respiratory arrest and death in healthy patients without the presence of anoxemia have been reported. There is some evidence that sensitized carotid sinus respiratory reflexes may have been involved.

Advantages and Uses of Nitrous Oxide. Nitrous oxide is non-toxic and the safest of all anesthetics. It is entirely non-irritating and has no untoward side-actions. The gas is not injurious to parenchymatous organs, and causes practically no metabolic disturbances in the body. Indeed, except for the fact that nitrous oxide is a relatively weak central nervous system depressant, it would qualify for the ideal gas anesthetic.

Nitrous oxide has proved of great value in dentistry, especially before the use of local anesthesia became commonplace. Nitrous oxide-oxygen mixtures (80:20) are useful for analgesia in labor, *when given by an expert anesthetist* so that an adequate supply of oxygen is constantly supplied both for the mother and child. The course of labor is not impeded.

A special use of nitrous oxide is for the rapid, pleasant and safe *induction of general anesthesia,* as in "gas-ether" sequence, first suggested in 1876 by Clover. It reduces anxiety and avoids the excitement stage of ether anesthesia. After induction with nitrous oxide, ether is gradually added while the nitrous oxide is withdrawn. The effects of ether and nitrous oxide are purely additive.

Disadvantages. The disadvantages of nitrous oxide are chiefly those of anoxia. Nitrous oxide given undiluted or with very low concentrations of oxygen is not satisfactory for any operation lasting longer than from thirty seconds to one and one-half minutes. When oxygen in sufficient concentration to prevent anoxemia is employed with nitrous oxide, the degree of muscular relaxation required in major surgical procedures is not easily obtained. Without adequate oxygen, the resulting cyanosis, acidosis, rise in blood pressure, tachycardia, etc., make nitrous oxide dangerous in patients with high blood pressure, cardiovascular disease and high metabolic rates. It is often impossible to anesthetize patients with high reflex excitability. Finally, nitrous oxide anesthesia necessitates special apparatus and an experienced anesthetist. It is clear, therefore, that the principal disadvantage of the gas is the fact that, being a weak anesthetic, it has a limited sphere of usefulness unless given with adequate oxygen and supplemented by proper preanesthetic medication, basal anesthesia or other anesthetic agents. The dangers of cerebral damage from anoxia incident to the use of nitrous oxide already have been presented (page 55).

ETHYLENE

Historical. Hermann (1865) was the first to note the anesthetic action of ethylene. Similar work was reported by Eulenberg (1876) and Luessem (1885) but no practical results were forthcoming until Crocker and Knight (1908) noted the toxicity for plants of ethylene in very high dilutions. In that year, certain carnation growers suffered heavy financial loss because the flowers shipped to Chicago "fell asleep" in the greenhouses and the buds failed to open. Crocker and Knight of the Hull Botanical Laboratory studied the illuminating gas used in the greenhouses and found ethylene, which comprised four per cent of the gas, to be the toxic agent. A dilution of 1:2,000,000 of ethylene in air is sufficient to affect carnations. The anesthetic action of ethylene on animals was rediscovered independently by Luckhardt and Lewis (1923) and by Brown (1924). Luckhardt and Lewis were active in the successful development of ethylene as a surgical anesthetic. Clinical surgery under ethylene anesthesia was first performed in 1923.

Chemistry. *Ethylene* (U.S.P., B.P.), $H_2C=CH_2$, is an unsaturated hydrocarbon of the olefin series. It is a highly volatile colorless gas which has a slightly sweet taste and not unpleasant odor. The gas is soluble in water 1:9 by volume, and has a boiling point of −103.9 C. Ethylene is lighter than air whereas ether and cyclopropane are heavier. It is furnished in compressed form in metal cylinders. For use as an anesthetic, ethylene is marketed free from impurities, the presence of which has caused several accidents. Ethylene is explosive and inflammable when present in oxygen mixtures of certain strength, though by itself it is not explosive and will not support combustion. Explosiveness is the greatest drawback to the use of ethylene.

Actions. Ethylene has the typical action of the methane anesthetic series. Ethylene-oxygen mixtures produce satisfactory anesthesia with practically no effect on vital functions. The innocuousness of ethylene for tissues is its outstanding advantage.

Induction. The speed of induction is rapid, exceeding that of nitrous oxide. After the patient has taken six or more deep inhalations, mental clouding supervenes and unconsciousness soon follows. Induction is not disagreeable, although an occasional patient (or surgeon) may complain of the odor of the gas. The purer samples are usually free of objectionable odor. Ethylene does not irritate the respiratory mucosa and hence reflex respiratory irregularities during induction are absent. When the pure gas is inhaled, however, a sense of suffocation is experienced and reflex choking or swallowing may occur. Bronchial secretions and salivation are not stimulated by ethylene.

Anesthesia. Full surgical anesthesia occurs in from two to five minutes. Ethylene is a more powerful anesthetic than nitrous oxide, but less powerful than cyclopropane or ether. Under favorable conditions, it can carry anesthesia to the lower border of plane i, that is, 25 per cent of the way through the third stage (Figure 4). This fact accords ethylene an anesthetic potency of 25 per cent in comparison with nitrous oxide which has a potency rating of 15 per cent (Guedel, 1937). It may be recalled that the agents possessing a 100 per cent potency rating are ether, chloroform, divinyl oxide and cyclopropane (page 50). Subanesthetic concentrations of ethylene, however, are definitely analgesic and the inhalation of 25 to 35 volumes per cent of ethylene produces analgesia without loss of consciousness or cooperativeness (Seevers and associates, 1937). On this basis, ethylene is only one-sixth as potent as cyclopropane, which requires but four to six volumes per cent, and slightly more potent than nitrous oxide, which requires 35 to 40 volumes per cent for analgesia.

The induction of surgical anesthesia requires 90 volumes per cent of ethylene, leaving only 10 volumes per cent of oxygen available. Unless the concentration of ethylene is at least 90 per cent to start with, it may be impossible to induce surgical anesthesia. Once surgical anesthesia is obtained, however, the concentration of ethylene may be reduced to 80 volumes per cent and the concentration of oxygen increased to 20 volumes per cent, without lessening the degree of anesthesia. This allows sufficient oxygen to prevent anoxia and acidosis. Ethylene anesthesia provides an excellent example of the value of preanesthetic medication. When this is adequate, full anesthesia can be induced with an 80:20 mixture. Anesthesia is usually induced, however, with a 90:10 mixture.

Muscular relaxation is more profound with ethylene than with nitrous oxide anesthesia, but much less so than with ether. Even with satisfactory preliminary medication, upper plane ii is rarely exceeded, and ethylene must be supplemented with a small amount of ether when operations requiring complete muscular relaxation are undertaken.

Respirations during surgical anesthesia under ethylene are quite normal, slow and regular. Ethylene is never a respiratory depressant by its own action, and it is thus impossible to produce respiratory paralysis by the action of ethylene alone. The medulla is not depressed; it may even be slightly stimulated by the lowered oxygen tension incident to the use of ethylene in concentrations over 85 volumes per cent. The *blood pressure* may rise moderately during the induction and early phase of surgical anesthesia, probably due to the slight anoxemia, but it soon returns to normal and remains there throughout the operation. The cardiac output may increase under ethylene anesthesia. Arrhythmias occur less frequently when ethylene is used than with any other general anesthetic (Kurtz and coworkers, 1936). The cardiovascular effects of the gas, therefore, are extremely benign. The isolated mammalian heart, for example, is unharmed when perfused with fluid saturated with the gas. Anoxemia during induction is very slight and insufficient to produce cyanosis. The *color* therefore remains good. The fall in body *temperature* is not as marked as with ether; there is no sweating, and salivation is negligible or absent. Pulmonary irritation does not occur and the secretion of *bronchial mucus* is not stimulated. Ethylene is thus often the anesthetic of choice for many types of thoracic operations, especially in patients with pulmonary disease. *Renal and hepatic functions* are unimpaired by the gas and the *metabolic changes* are insignificant when anoxia is avoided. *Acidosis* occurs less often with ethylene than with ether or chloroform. The respiratory mechanism of the fetus is not depressed when ethylene is used in obstetrics, nor is uterine activity impaired.

Recovery. Recovery from anesthesia is quite rapid. As a rule, the patient is awake with a clear mind and able to talk within two or three minutes after cessation of administration of the gas. In fact, so rapid are induction and recovery that the constant attention of the anesthetist is required to maintain even anesthesia in the desired plane. Speedy recovery with quick restitution of the cough reflex is especially important in chest surgery or pulmonary disease. Ethylene is excreted almost quantitatively in the exhaled air and undergoes no chemical changes in the body.

Postanesthetic nausea or vomiting is somewhat less frequent and less severe than after ether, the incidence with ethylene being 33 per cent as compared with 57 per cent for ether (Waters, 1936). Gas pains likewise are milder and less frequent after ethylene, and the incidence of postoperative distention is only seven per cent as compared with 16.5 per cent for ether. The entire intestinal musculature is stimulated rather than depressed with light ethylene anesthesia, and remains normal during deeper planes of anesthesia.

Preanesthetic Medication. Preliminary medication for ethylene anesthesia does not differ from that used for other inhalation anesthetics, and is practically indispensable. By decreasing the amount of ethylene needed, it permits a greater percentage of oxygen in the mixture, and by reducing the patient's reflex irritability, a deeper plane of anesthesia can be reached. Furthermore, smooth induction is facilitated.

Advantages. Ethylene has many advantages as an anesthetic agent. It allows a rapid, pleasant and safe induction. Excitement and struggle are minimal or absent. There is practically no induction asphyxia. Recovery from anesthesia is rapid and postoperative complications are relatively infrequent. Respiratory and vasomotor depression and metabolic disturbances are not encountered. Pulmonary and renal irritation are absent, and salivary and bronchial secretions are not troublesome. Sweating is not produced and thus water loss and fall in body temperature are not pronounced. More complete muscular relaxation is possible with ethylene than with nitrous oxide. The advantages of ethylene have been reviewed by Guthrie and Woodhouse (1940) on the basis of their experience with the gas in over 35,500 anesthesias.

Fatalities. Death from concentrations of ethylene employed in clinical anesthesia is extremely rare. In order to increase the concentration of the gas to the point of toxicity, the oxygen must be so greatly reduced that the resulting symptoms are almost entirely the result of asphyxia. It is difficult to kill animals with ethylene *per se* unless the pressure of the gas is increased. For example, under two atmospheres pressure, 70 volumes per cent of ethylene (partial pressure 1064 mm) are required to kill mice when adequate oxygen is present.

Disadvantages. The chief disadvantage of ethylene is that it is explosive in certain oxygen mixtures. Accidents with fatalities have occurred, especially in the early days of the use of ethylene, and certain hospitals do not permit the use of this gas. However, the present precautions against explosions are quite sufficient, and include the strict avoidance of flames and sparks, the use of the cautery only under definite restrictions, and the humidification of the atmosphere to at least 60 per cent saturation. Ethylene-nitrous oxide mixtures are violently explosive, and if the gases are used together the two cylinders should never be opened at the same time. The explosive range of ethylene-oxygen mixtures is broad, the most dangerous mixture being from five to 25 per cent ethylene diluted with air or oxygen. Therefore, the most critical time is at the end of anesthesia when ethylene is discontinued. The exhaled mixture remains in the explosive range for three to four minutes after ethylene is stopped. The usual anesthetic concentration for induction, 90:10, is beyond the explosive limits because ethylene-oxygen mixtures do not ignite if the ethylene concentration is above 80 or below 2.5 per cent. Nevertheless, the anesthesia should be conducted at all times as if an explosive mixture were being handled.

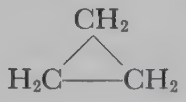
Ethylene provides less muscular relaxation than is obtainable with ether. This is not a serious disadvantage, however, for with proper preliminary medication or slight amounts of supplemental ether, deeper planes of surgical anesthesia are possible. A special gas apparatus is needed for ethylene anesthesia, as is also an anesthetist who has had considerable experience with the gas.

Special Uses. In addition to the usefulness of ethylene anesthesia for general surgical procedures, it may be of special value in obstetrics. *Obstetrical analgesia,* sufficient in degree until the presenting part distends the vulva, is possible with only 25 to 50 per cent ethylene in air. Ethylene does not inhibit uterine activity during labor (Rucker, 1926). The incidence of fetal asphyxia is only one-half that experienced with nitrous oxide-oxygen obstetrical analgesia. Some believe, however, that ethylene increases post partum bleeding. The intermittent administration of ethylene in labor to control pain entails a serious danger of explosion. The entire explosive range of the gas is passed through during each induction or emergence from ethylene analgesia and the frequent application and removal of the mask invites the production of a static spark between the mask and the patient's face. Several fatal explosions have occurred in this manner. Ethylene has been employed in *encephalography,* the gas being injected in the subarachnoid space in place of air.

CYCLOPROPANE

Historical. Cyclopropane was first prepared and described as trimethylene in 1882 by von Freund, but its anesthetic properties were not appreciated. Years later, propylene ($CH_3 \cdot CH:CH_2$), an isomer of cyclopropane, was studied extensively for its usefulness as a general anesthetic but it was found to be too toxic for the heart. In searching for the cause of this toxicity, Lucas and Henderson (1929, 1930) tested cyclopropane as a possible impurity. Cyclopropane was not only exonerated from being the cause of the toxicity of propylene but was found in itself to be a safe and potent anesthetic agent. The first clinical reports came from the Department of Anesthesia at the University of Wisconsin General Hospital after a three year period of study and clinical trial (Waters and Schmidt, 1934).

Chemistry and Preparations. *Cyclopropane,* U.S.P. XI (1939 Supplement), is the simplest possible cyclic hydrocarbon, with the following structural formula:



Cyclopropane

Cyclopropane is a colorless gas with a mildly pungent but not unpleasant odor and taste. In anesthetic concentrations, it is odorless. It is stored in metal cylinders as a liquid under pressure, and remains quite stable. Cyclopropane is heavier than air, and is inflammable and explosive. The explosive range of cyclopropane in air is 3.0 to 8.5 per cent; in oxygen, 2.5 to 50 per cent.

Effective Anesthetic Concentrations. Cyclopropane is the most potent of the anesthetic gases. It can cause analgesia without unconsciousness if continuously inhaled in a concentration as low as three to five volumes per cent (Seevers and associates, 1937). The average concentration of cyclopropane in the respiratory tract as determined by gas analyses during various planes of surgical anesthesia in man is as follows (Waters and Schmidt, 1934): plane i, 7.4 per cent; plane ii, 13.1 per cent; plane iii, 23.3 per cent; plane iv, 42.9 per cent. These anesthetic concentrations apply when preliminary medication with morphine has been given. Without preliminary morphine, for example, 26 volumes per cent of cyclopropane are needed to produce plane ii. These data provide another example of the value of preanesthetic medication.

Two important clinical advantages are immediately apparent. A wide margin of safety exists between the anesthetic and toxic concentrations of the gas (13 per cent vs. 43 per cent). The concentration of cyclopropane required for anesthesia is so low that the oxygen content of the anesthetic mixture can always be 20 per cent or more. Even with air as a vehicle, adequate oxygenation of the tissues is possible; but oxygen is ordinarily used as the diluent.

Anesthetic Actions. *Induction.* Induction with cyclopropane is pleasant, more rapid than with ether, but less so than with nitrous oxide or ethylene. Unpleasant subjective sensations are eliminated by the use of sufficient oxygen and the "head fullness" noted with nitrous oxide is absent. Cyclopropane is not irritating to the respiratory tract and therefore respiratory irregularities do not occur. Salivation is not prominent. Laryngospasm develops only with higher concentrations than are ordinarily required. Although cyclopropane is a gas like nitrous oxide and ethylene, it has the anesthetic potency of chloroform, and the anesthetist must therefore be on guard not to rush the patient from one stage to another.

Unconsciousness occurs in from 20 seconds to three minutes. In about five minutes plane ii of stage III is reached. Cyclopropane does not cause dreams as does nitrous oxide or ethylene.

Physical Signs. Physical signs during cyclopropane anesthesia are similar to those with other anesthetics, except for the following features concerning respiration. (1) The patient can breathe an anesthetic concentration of cyclopropane without respiratory irritation or laryngospasm, as the gas is without irritating properties. This means that the normal physiological protections (coughing, apnea, laryngospasm, struggle) against a sudden increase in concentration are absent. (2) Cyclopropane is not a respiratory stimulant and does not cause an initial increase in the rate and minute volume of respiration as do ether, nitrous oxide and ethylene. Therefore no change in respiration is noted with cyclopropane until the onset of respiratory depression (Figure 8). (3) Diaphragmatic breathing in plane iii is not exaggerated nor is the respiratory rate elevated with cyclopropane as with other anesthetics. Therefore one must watch closely the rebreathing bag in this plane for the first evidence of impending apnea of plane iv.

Danger Signals. Not only does the respiration fail to provide useful physical signs incident to deep anesthesia, but certain less important danger signals are obscured by cyclopropane anesthesia. These are the pupillary changes and the color of the skin.

The value of the *pupils* in judging the depth of anesthesia is diminished by the preliminary administration of morphine and atropine. Despite the action of these alkaloids, with most anesthetics the pupils usually dilate as anoxia develops in lower plane iii. When preanesthetic medication is used with cyclopropane, however, only slight and late pupillary dilatation occurs. Even the fourth stage of anesthesia is often entered without pupillary changes, and dilatation is not marked until the reserve oxygen of the tissues is depleted after respiratory arrest. Without preliminary medication, pupillary dilatation may occur with cyclopropane in the lower third or upper fourth plane.

The *color of the skin* cannot be used as an index of danger during cyclopropane anesthesia because oxygen is given in sufficient excess so that the skin is pink at all times.

The *pulse changes* are the best warning indices with cyclopropane. Arrhythmias, slowing of the heart to 50 beats or less per minute, or definite tachycardia should warn the anesthetist to decrease the concentration of cyclopropane.

Respiration. Certain aspects of respiration have already been discussed. Breathing is very quiet throughout anesthesia. No depressant effect is seen even with deep surgical anesthesia (Figure 8). When apnea occurs in plane iv, a reduction in cyclopropane is sufficient to restore breathing. The high oxygen tension and quiet respiration characterizing cyclopropane anesthesia may make massive atelectasis difficult to detect, and deaths have occurred from this complication (Jones and Burford, 1938). Indeed, cyclopropane-oxygen anesthesia may possibly contribute to the atelectasis by the loss of non-absorbable sustaining nitrogen from the lungs (page 53). Atelectasis may then result from the complete absorption of cyclopropane and oxygen from the distal alveoli during the deeper levels of anesthesia, when the respiratory volume is decreased, and after the sudden withdrawal of the anesthetic mixture at the termination of anesthesia. It has therefore been suggested (Burford, 1938) that some slowly absorbed inert gas such as helium be used in the anesthetic mixture in order to prevent alveolar collapse.

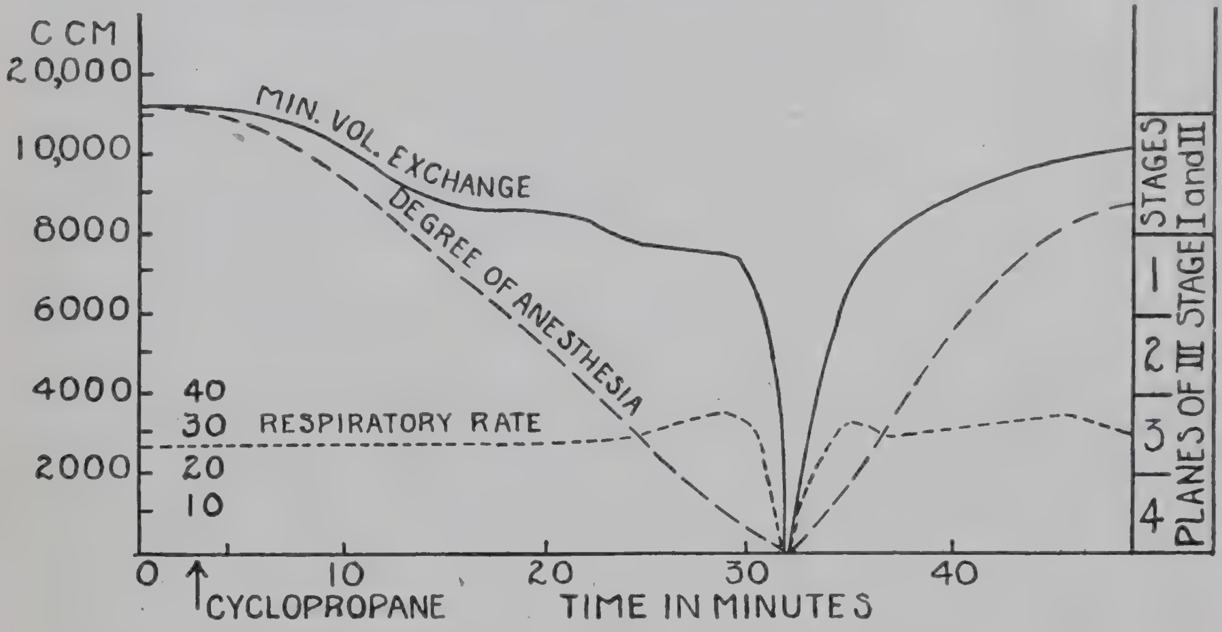


Figure 8. *The effect of cyclopropane anesthesia on respiration in man.*

Tidal exchange and respiratory rate were measured by means of a water spirometer arranged in the closed circuit to record on a kymograph. Minute volume exchange was calculated from these data. Anesthesia was purposely induced gradually and the various stages and planes were passed through slowly so that the point of respiratory arrest was reached in 28 minutes. Cyclopropane was then stopped and pure oxygen administered, and respiration was resumed spontaneously within 30 seconds.

Observe that no increase in rate or tidal volume of respiration occurred after cyclopropane anesthesia was started. Rather, a very gradual decrease in depth but not in rate occurred until intercostal paralysis of plane iv was reached, at which point an increase in rate began which was insufficient to maintain efficient respiratory exchange. Thus, cyclopropane causes no stimulation of breathing during induction, and only slight depression as anesthesia advances, until a concentration is reached which shortly will result in respiratory arrest. (After Waters, 1936. Courtesy of the *British Medical Journal.*)

The absence of respiratory depression during cyclopropane anesthesia is a distinct advantage to the mother and child in obstetrical procedures. In this connection, Rosenfeld and Snyder (1939) studied the respiratory depressant effects on rabbits at term of a number of agents (pentobarbital, morphine, paraldehyde, chloral hydrate, ether, nitrous oxide and cyclopropane). Only cyclopropane produced full surgical anesthesia in the mother without depressing or abolishing fetal respiration.

Cardiovascular System. Anesthetic concentrations of cyclopropane have little effect on the *blood pressure.* The rises which occur are probably related to carbon dioxide retention, anoxia or pressor reflexes, and are not seen if these factors are avoided (Seevers and Waters, 1938). Cyclopropane tends to dilate peripheral vessels and capillary oozing may be increased. The cardiac rate is usually slowed somewhat during stage III.

Arrhythmias of various types have been reported. Kurtz and coworkers (1936) recorded electrocardiographically the occurrence of ventricular extrasystoles in 56 per cent of a series of 41 patients given cyclopropane anesthesia (Figure 9) but approximately half of the patients had heart disease. Waters (1936) has reported from analysis of a large series of anesthetic administrations that cyclopropane causes a higher incidence of arrhythmia (detectable by palpation of the pulse) than does ether. The relative incidence in different planes of anesthesia is shown in Table 2, a study of which indicates that cyclopropane differs from ether (and chloroform) in that cardiac arrhythmias are more apt to occur as the depth of cyclopropane anesthesia increases. This agrees with the observations of Meek and collaborators (1937) who found that epinephrine caused tachycardia of ventricular origin in the dog more readily under deep than under light cyclopropane anesthesia.

TABLE 2

INCIDENCE OF ARRHYTHMIAS *

(Waters, 1936.)

	CYCLOPROPANE			ETHER		
Stage III	Cases	Number	%	Cases	Number	%
Plane i	635	13	2.22	31	2	6.45
Plane ii	1263	72	5.70	275	7	2.54
Plane iii	471	37	7.86	305	8	2.62
Plane iv	298	38	12.72	115	2	1.74
Total	2667			726		

* As detected by palpation of the pulse.

Probably the most common form of arrhythmia seen under cyclopropane is *ventricular tachycardia.* For this reason, premature operative stimuli and epinephrine should be strictly avoided because of the possible danger of causing ventricular fibrillation. Indeed, Meek and associates (1937) found that tachycardia of ventricular origin in the dog was more readily induced by an injection of epinephrine during cyclopropane than during ether or chloroform anesthesia. Also, Orth and coworkers (1939) demonstrated that epinephrine and a number of related sympathomimetic amines so sensitize the ventricular automatic tissue of dogs that cyclopropane anesthesia then causes multifocal ventricular tachycardia. It is generally agreed that clinical arrhythmias are especially likely to occur with an excessive concentration of cyclopropane or when anoxia is present. Kurtz and coworkers (1936) purposely carried cyclopropane anesthesia to plane iv in 41 patients and noted four instances of "multiple focus ventricular tachycardia." This type of disorder is similar to that noted by Hill (1932) during chloroform anesthesia in man (page 62), and by Levy (1914) preceding ventricular fibrillation due to chloroform anesthesia in cats. Waters (1936) records that two of three deaths occurring during 7200 administrations of cyclopropane were probably due to ventricular fibrillation.

Although arrhythmias, including ventricular tachycardia, extrasystoles and A-V blocks, have been produced experimentally in animals under cyclopropane anesthesia, there is no clinical or laboratory evidence to indicate that the disturb-

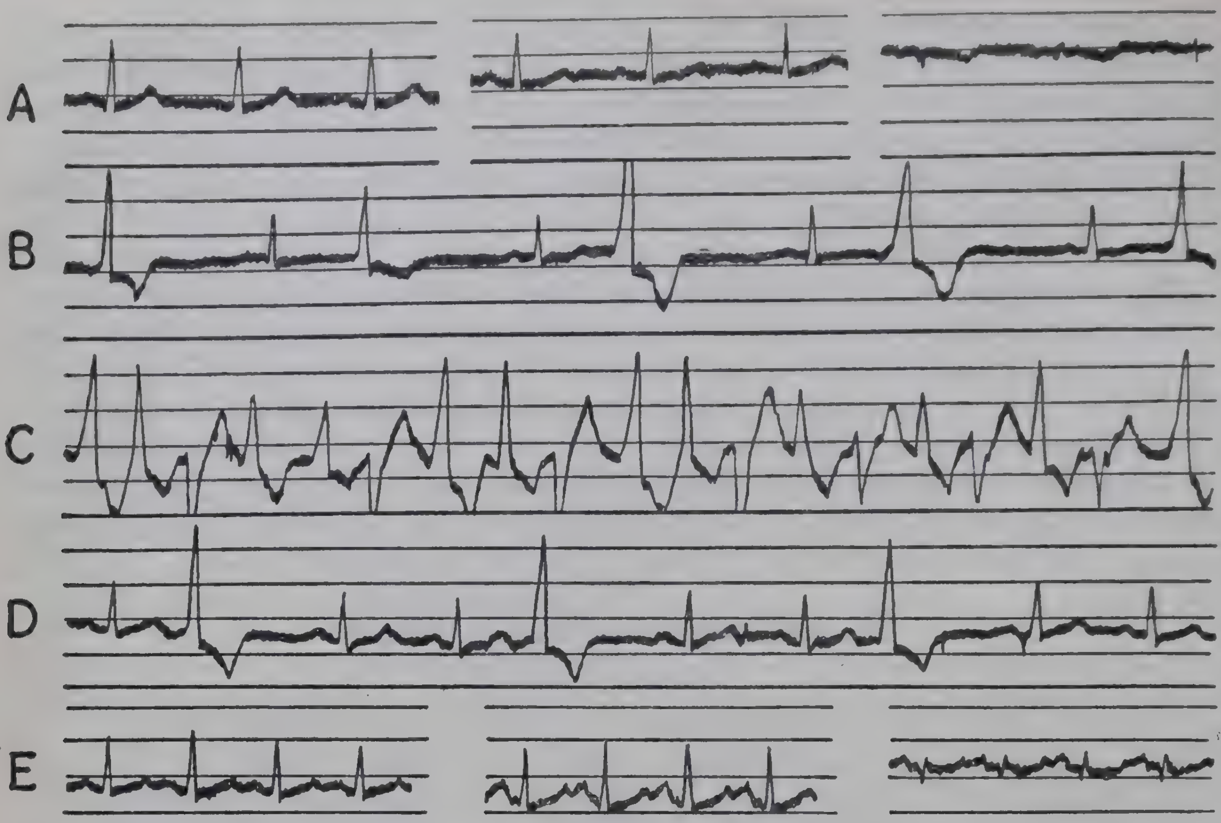


FIGURE 9. *Electrocardiographic abnormalities caused by cyclopropane anesthesia.*

Woman, aged 32, with a normal heart; pelvic operation. *A.* Before operation: normal tracing in leads I, II and III. *B.* First plane anesthesia, 10 minutes after induction and during preparation of operative field: lead II shows ventricular extrasystolic rhythm. *C.* First plane anesthesia, 36 minutes after induction, during exploration of abdomen: lead II shows multiple focus ventricular tachycardia. *D.* First plane anesthesia, 43 minutes after induction: ventricular extrasystoles. *E.* Ten hours after operation: normal sinus rhythm restored. (After Kurtz, Bennett and Shapiro, 1936. Courtesy of *The Journal of the American Medical Association.*)

ance is other than functional and transitory. Myocardial injury could not be detected in dogs by anesthetic concentrations of the gas sufficient to cause respiratory arrest (Meek and Volpitto, 1936), and the cardiac output is considerably increased under moderate cyclopropane anesthesia (Robbins and Baxter, 1938).

It has been suggested by Robbins and his associates (*see* Robbins, 1940) that the character of the preanesthetic medication employed prior to cyclopropane anesthesia may be an important factor in determining the occurrence of cardiac irregularities. For example, in dogs without preanesthetic medication and under artificial respiration, the cyclopropane concentration of the blood can be increased approximately 30 per cent over that required for respiratory arrest without the occurrence of electrocardiographic changes. After preanesthetic medication with morphine, the same types of electrocardiographic abnormalities occur in dogs during cyclopropane anesthesia as those most frequently observed clinically. However, when barbiturates are administered prior to cyclopropane, cardiac arrhythmias do not occur until long after respiratory arrest. Inasmuch as morphine is frequently administered before cyclopropane anesthesia in human beings, it is important to determine whether this alkaloid is a factor in the arrhythmias described.

In *summary,* it may be stated that clinical experience has shown cyclopropane, administered expertly, to be a safe agent as regards the cardiovascular system, even in cases of bad risks and cardiovascular disease. Experimentally, however, there is evidence to indicate the occurrence of sensitization of the automatic tissue of the heart and arrhythmias of a transitory and purely functional nature. Although disturbances of rhythm during both general and local anesthesia occur far more often than is generally recognized (only 21 per cent of 109 cases of anesthesia by various agents studied by Kurtz and associates [1936] failed to show irregularities), nevertheless the cardiac effects of cyclopropane deserve further study. The actions of cyclopropane anesthesia on the circulatory system have been extensively reviewed by Robbins (1940).

Muscular Relaxation. As a rule, muscular relaxation is quite sufficient for most operations; indeed, cyclopropane has been used in every type of surgical procedure, including obstetrical surgery. In some difficult abdominal operations, a small amount of supplemental ether may be necessary.

Metabolic Effects. Extensive studies of the blood and urine, and of functions of the kidneys and liver show no deleterious effects of cyclopropane. The functional capacity of the liver is not depressed (Raginsky and Bourne, 1934). No significant changes are noted in the blood levels of non-protein nitrogen or sugar or in CO_2-combining power during or after clinical anesthesia with cyclopropane, either in the normal or diabetic patient (Waters and Schmidt, 1934; Neff and Stiles, 1936; Robbins, 1940).

Recovery. Recovery from cyclopropane anesthesia occurs with the same speed as from nitrous oxide and ethylene, that is, within a few minutes after cessation of anesthesia. Nausea and vomiting are less severe and less frequent than after ether but more common than after nitrous oxide and ethylene. The same is true of postoperative distention (Waters, 1936). Pneumonia and atelectasis are much less common than after ether. Schmidt and Waters (1935) noted fewer respiratory complications in over 2000 patients anesthetized with cyclopropane than in an equal number of cases anesthetized with other anesthetics. Tachycardia and severe postoperative fall in blood pressure are perhaps more frequent with cyclopropane than with ether, but the absolute incidence is low. Headache apparently occurs more commonly during recovery from cyclopropane than from other general anesthetics.

Technic of Administration. A closed circuit method is used for cyclopropane, and a modernly constructed or adapted gas-oxygen machine is required. The patient rebreathes an oxygen-cyclopropane mixture, and the exhaled carbon dioxide is absorbed. A constant metered flow of oxygen replaces the oxygen consumed and more cyclopropane is added to the mixture as it is needed. When the desired plane of anesthesia is reached and muscular relaxation is adequate, the flow of cyclopropane is discontinued and the patient rebreathes the existing mixture. Often a pharyngeal airway is used with cyclopropane; some anesthetists prefer the use of an endotracheal airway fitted with an inflatable tracheal cuff, thus dispensing with the face mask. The cost of cyclopropane for the average operation is about 50 cents per hour, during which time one gallon of the gas is used.

Preanesthetic Medication. Atropine or scopolamine is essential before cyclopropane anesthesia in order to reduce the slight amount of mucus secretion which otherwise would occur. Some anesthetists prefer to use avertin for basal anesthesia and cyclopropane as the supplemental agent. In fact, Wood (1936) believes this type of combined anesthesia approaches the "mythical ideal" and that the surgical mortality and morbidity are lower than with any other anesthetic agent. Accurate timing of preanesthetic medication is essential to this technic. Not over 10 mgm of morphine are given with 0.4 mgm atropine one hour before avertin. Avertin is then administered in the dose of 60 to 80 mgm per kg, 30 or 40 minutes prior to cyclopropane. Only rarely are small amounts of ether needed for more complete muscular relaxation. When morphine or barbiturate is employed prior to cyclopropane anesthesia, the concentration of gas needed for a given plane of surgical anesthesia is considerably reduced, as aforementioned (*see also* Robbins, Baxter and Fitzhugh, 1939).

Absorption and Excretion. Cyclopropane is rapidly absorbed and eliminated. It is entirely excreted from the body by way of the lungs. At the time of awakening, the concentration of cyclopropane in the expired air has fallen to one per cent and only traces are found at the end of three hours.

Advantages. Cyclopropane allows more than adequate oxygen throughout all depths of anesthesia. It is nonirritating and does not cause respiratory irregularities in stage II. Anesthetic concentrations do not depress the heart or circulation. Salivation is not prominent. Deleterious metabolic effects are singularly absent. Liver injury, as measured by the bromsulfalein dye excretion test, does not occur. Postanesthetic recovery is rapid and smooth, with less nausea and vomiting, less postoperative distention and fewer respiratory complications than after ether. The reports of Taylor and associates (1937) and Burford (1938) indicate that postoperative pulmonary complications occurred in less than one per cent of over 7000 cyclopropane administrations, but the incidence is closer to two per cent when calculated only on the basis of abdominal operations. Cyclopropane produces greater muscular relaxation than does any other anesthetic gas, although third plane anesthesia may be necessary to obtain the desired degree. Finally, there is a wide margin of safety between anesthetic and toxic concentrations, perhaps wider than that existing for any other anesthetic agent now in use.

Disadvantages. Cyclopropane is explosive and inflammable within the entire range of anesthetic mixtures. It is less explosive, however, than ethylene or nitrous oxide-ether mixtures. Great care must be observed if the cautery or electric knife is employed during anesthesia with cyclopropane, and while they are being used, no gas should be released from the breathing bag. Fat burns with a more active flame during cyclopropane anesthesia than during ethylene anesthesia, due to the high percentage of oxygen present. After the administration of cyclopropane is stopped, the exhaled air is still inflammable for from six to eight minutes. Anesthesia with cyclopropane requires a completely closed circuit with a carbon dioxide absorption system, both for safety and economy. The cost of the gas would be prohibitive unless a closed system were used. Cyclopropane must be given by an experienced anesthetist. Some surgeons claim that cyclopropane produces capillary oozing, although others deny this. Lastly, the status of cyclopropane in regard to its effects on the heart has not been finally determined, and the gas should be avoided in patients in whom the use of epinephrine during anesthesia is anticipated.

Indications and Uses. Cyclopropane has been successfully employed in every type of surgical operation. It is especially useful when maintenance of tissue oxygenation is of paramount importance, as in pregnancy and in patients with exophthalmic goiter, congestive heart failure, grave circulatory complications, anemia, and pulmonary disease or respiratory obstruction. Cyclopropane anesthesia is particularly valuable in chest surgery because of the quiet respirations, plenitude of oxygen, absence of laryngospasm and bronchial irritation, and quick recovery of the cough reflex (Eversole and Overholt, 1936; Rovenstine, 1935). In obstetrical procedures, the gas may be employed for analgesia or anesthesia.

The fact that cyclopropane has no depressant action on the respiratory system of the mother and child is a definite advantage, and uterine activity is not depressed (Bourne, 1934).

ACETYLENE

Acetylene is a colorless, highly volatile and explosive gas with a pungent ethereal odor, and possesses the typical action of the methane series of anesthetics. Its formula is $HC \equiv CH$. Commercial acetylene contains impurities which produce toxic effects and even the pure gas must be passed through water or over activated carbon to remove the acetone in which the acetylene is stored in solution. Even when pure, acetylene has a disagreeable odor. Anesthesia in man requires approximately 60 to 80 volumes per cent of the gas, but muscular relaxation is not adequate in the majority of patients and plane iii is not obtainable without anoxia. Although acetylene once enjoyed some use as a surgical anesthetic agent in Europe, it has not been employed to any extent in the United States. It is more explosive and not as satisfactory an anesthetic as ethylene, the gas which it most closely resembles.

Acetylene is not metabolized by the body, and is rapidly absorbed and excreted by the lungs. It has been found serviceable as a gas for the determination of cardiac output (Grollman, 1932).

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CHAPTER 7

BASAL ANESTHETICS

TRIBROMETHANOL

(AVERTIN)

Historical. Tribromethylalcohol was introduced in 1926 by Willstaetter and Duisberg as a "fixed-dose" anesthetic for rectal administration. Its main use today is for basal anesthesia, expert anesthetists agreeing that it should not be employed alone for full surgical anesthesia. Avertin has been widely used as a basal anesthetic and sufficient clinical data are available to allow a proper evaluation of its uses and dangers. *Avertin with Amylene Hydrate* (N.N.R.) is the Council-accepted preparation.

Chemistry and Preparations. *Tribromethanol,* CBr_3CH_2OH, is closely related chemically to chloral (CCl_3CHO) and to ethyl alcohol (CH_3CH_2OH), three bromine atoms being substituted in the latter to produce avertin. Bromination of ethyl alcohol greatly increases the anesthetic action of the drug, another example of the increase in anesthetic potency resulting from halogenation of an aliphatic hydrocarbon. The bromide ion as such does not contribute to the depressant action, because tribromethanol does not dissociate in the body to any extent. Traces of bromine, however, may be found in the breath and sweat (Parsons, 1931) after the administration of the drug.

Avertin is a white crystalline powder with a slight aromatic odor and taste. It decomposes slowly at room temperature and rapidly above 40 C. Its aqueous solubility is rather low (1:35) and therefore the drug is marketed as *Avertin with Amylene Hydrate* (N.N.R.) (formerly called Avertin-Liquid), a solution of avertin in a special liquid solvent, *amylene hydrate.* Because the solvent is volatile and avertin decomposes on exposure to light, the solution should be kept in well-stoppered brown bottles. Amylene hydrate is also inflammable.

Amylene Hydrate. Amylene hydrate is a central nervous system depressant, but plays a minor rôle in the anesthesia produced by avertin with amylene hydrate. One cc of this solution contains one gram of avertin and one-half gram of amylene hydrate. In the following discussion, whenever the dose of avertin is given, it refers to avertin with amylene hydrate and therefore one-half of the same weight of amylene hydrate is automatically included. In describing the actions of avertin, the combined effects of avertin and amylene hydrate are being considered.

Amylene hydrate, introduced as a sedative by Harnack and Meyer in 1894, is a tertiary amyl alcohol, $(CH_3)_2C(OH)C_2H_5$. It ranks between chloral hydrate and paraldehyde in hypnotic properties, and is fairly nontoxic. It is a colorless fluid, soluble in eight parts of water, and readily soluble in glycerin. The hypnotic dose is one to four grams, administered in glycerin, but the drug is almost never used clinically for the purpose of sedation. The amount of amylene hydrate contained in avertin with amylene hydrate given to a 60 kg man, at the dose level of 80 mgm of avertin per kg, is only 2.4 grams, and therefore the depressant action of the solvent *per se* cannot contribute much to the anesthesia.

Actions. Avertin has the typical depressant action on the central nervous system of the methane series of anesthetics.

Induction. Induction of anesthesia following the rectal administration of avertin is fairly rapid and quite pleasant, and usually there is little or no excitement stage. The patient often merely "falls asleep" within five to 15 minutes, without being disturbed by a face mask, machinery or unpleasant vapors. The anesthetic can be given in the patient's room, often without telling him that he is being prepared for surgery. This feature is sometimes of great value in the thyrotoxic patient, to whom the rectal anesthesia can be administered as a "routine enema."

Basal Anesthesia. Maximal basal anesthetic action is reached in from 20 to 30 minutes, at which time the concentration of avertin in the blood is from six to 10 mgm per cent. The anesthesia becomes lighter by the end of one hour, and consciousness is regained in from one and one-half to three hours, at which time the concentration of avertin in the blood has fallen to two or three mgm per cent. Awakening is usually followed by a long postoperative sleep, lasting for several hours, and complete amnesia exists for this entire period.

Muscular Relaxation. The muscular relaxation obtained with avertin varies with the dose of anesthetic given. It is quite complete with large doses which produce deep surgical anesthesia, but is only partial with safe doses which produce only plane i anesthesia. Excellent relaxation occurs when slight amounts of supplemental ether or cyclopropane are used with basal anesthetic doses of avertin.

Circulation. Avertin usually causes an early, rather marked but temporary fall in blood pressure, which varies from 15 to 40 mm of mercury, averaging about 25 mm. Occasionally, as in cases of hypertension, the systolic pressure may fall 100 mm of mercury. The hypotension lasts only five to 15 minutes and is rarely dangerous. It may easily be combated with ephedrine which may in certain cases be given prior to the avertin. The decline in blood pressure is due to depression by avertin of the medullary vasomotor centers, as well as to some degree of direct depressant action on the heart and blood vessels. Myocardial depression due to avertin is clinically negligible when basal anesthetic doses are employed. Perfusion experiments indicate that the drug is only one-sixteenth as toxic as chloroform to the mammalian heart.

Respiration. The respiration is markedly depressed by full anesthetic doses of avertin, and respiratory arrest is the major danger in avertin anesthesia. The usual cause of death with avertin is respiratory paralysis; but, when proper doses for basal anesthesia are given, avertin rarely causes serious respiratory embarrassment. Avertin is a solid anesthetic and there is no rapid way in an emergency to reduce its concentration in the body. Once given, it is beyond the fine control of the anesthetist. It is thus not safely used alone for complete surgical anesthesia, but is employed mainly for basal anesthesia with supplemental ether, nitrous oxide or cyclopropane. When breathing ceases, due to overdosage, artificial respiration can do no more than maintain oxygenation of the blood and does not, as is the case with volatile anesthetics, promote the pulmonary excretion of the toxic agent. Because of respiratory depression arising from avertin, preliminary morphine should not be used unles given in small doses (eight mgm) fully one and one-half hours beforehand. If the depression of breathing due to basal anesthesia with avertin is marked, pulmonary exchange may be too greatly diminished to allow induction of the proper plane of surgical anesthesia with an inhalation anesthetic (page 37) unless carbon dioxide is administered. It should be a rule not to use avertin as a basal anesthetic unless a person capable of intubating the trachea is available (Beecher, 1938).

Avertin tends to produce marked relaxation of the jaw muscles and obstruction of the airway may result. A rubber or metal airway should be inserted as soon as basal anesthesia is complete and not removed until the patient fully awakens.

Metabolic Effects. When avertin is used for basal anesthesia, the metabolic disturbances are mild as a rule. The body temperature is somewhat lowered, the blood sugar slightly elevated, and the CO_2-combining power of the blood slightly decreased. The basal metabolic rate is lowered by an average of 15 per cent.

Liver. Doses of avertin used in basal anesthesia have little serious effect on the normal liver. A detectable functional deficiency, as determined by the bromsulfalein dye excretion test, however, can be shown to occur more frequently after avertin than with ether or nitrous oxide anesthesia (Coleman, 1938). Large doses of avertin in normal persons, or smaller amounts in patients with liver disease, may possibly cause hepatic damage. In animal experiments, large repeated doses are required to produce liver damage which is only moderate in degree and reversible (Bourne and Raginsky, 1931). Although avertin has been given to jaundiced patients with apparently no ill consequences, by far the safest procedure is to limit its use to those with normal liver function. The rôle played by the healthy liver in detoxifying tribromethanol and removing it from the tissues is emphasized by the perfusion experiments cited by Beecher (1938). A 420 gram normal liver of a dog reduced the blood concentration of avertin from 130 mgm per cent to six mgm per cent in 90 minutes, whereas a liver in which fatty degeneration was experimentally produced was only about half as efficient. This is in agreement with the clinical finding that dangerously prolonged anesthesia may occur from avertin in patients with disease of the liver.

Kidneys. Avertin may cause albuminuria and frank renal injury may occur if the drug is used in patients with renal disease. Abnormally long and deep anesthesia may result if avertin is employed when renal function is poor because the kidneys represent the obligatory route of excretion. Renal insufficiency lowers considerably the margin of safety of the drug (Veal and coworkers, 1931).

Postanesthetic Recovery. Recovery from avertin anesthesia is pleasant as a rule, the patient awakening as from sleep. Nausea and vomiting are less frequent than with ethylene or ether, the incidence being about 22 per cent (Wood, 1936).

Absorption, Fate and Excretion. The rectal absorption of avertin dissolved in amylene hydrate is rapid. Fifty per cent is absorbed within 10 minutes, 75 per cent within 20 minutes, 85 per cent within 25 minutes and from 90 to 95 per cent within two hours. These figures, however, represent only approximate averages because the rate of absorption varies widely. For example, Sebening (1932) found that one patient absorbed 38 per cent within 10 minutes; another only 11 per cent within 60 minutes; the first subject absorbed a total of 80 per cent, the second only 29 per cent. When it is appreciated that the anesthetic action depends more on the rapidity of absorption than on the final amount absorbed, the variation in response to avertin can readily be understood. Avertin is combined with glycuronic acid in the liver, and its detoxification is therefore impaired when hepatic function is diminished. This constitutes another reason for caution in using avertin in patients with any suggestion of liver damage.

Avertin-glycuronate is excreted quantitatively by the kidneys, and quite rapidly. Excretion lags only slightly behind absorption and the drug is almost entirely eliminated by the end of two hours. Therefore avertin cannot be used alone for prolonged operations. If kidney function is poor, excretion may be considerably delayed and the toxicity of avertin correspondingly enhanced. Nephritis therefore is a definite contraindication to the use of avertin.

Administration and Dosage. *Preliminary Medication.* Atropine and morphine are usually given prior to avertin, but the dose of morphine must be reduced to eight or 10 mgm and given one and one-half hours before the avertin. Some believe that scopolamine should not be employed with morphine prior to avertin.

Dosage. Proper dosage is all important in the safe use of avertin for basal anesthesia. In the average case, a dose of 50 to 60 mgm per kg of avertin causes drowsiness, sleep, and amnesia; 70 to 80 mgm per kg results in light unconsciousness and analgesia; 90 to 100 mgm per kg causes complete anesthesia with varying degrees of muscular relaxation and loss of reflexes. The last mentioned dose, however, results in satisfactory surgical anesthesia in only 20 per cent of patients. Doses of 125 to 150 mgm per kg raise this figure only to 50 or 60 per cent. Inasmuch as the range of safe dosage extends only to 100 mgm per kg, it is clear that avertin alone should not be used for complete surgical anesthesia. Even the dose of 100 mgm per kg may sometimes produce complete and not basal anesthesia. The Council (1937) has recommended a dose of 80 mgm per kg as the ordinary maximum.

Total dosage, as a rule, is based on the weight of the patient. Some anesthetists, however, use the surface area of the body in calculating the dose. Charts are available for rapidly ascertaining the dose on the basis either of body weight or surface area, but these charts should not replace the anesthetist's judgment as to the special needs of the particular case. Regardless of the patient's weight, a total dose of nine to 10 grams for men, or six to eight grams for women is not exceeded. Dosage is reduced for elderly or cachectic patients, and is never over 60 to 80 mgm per kg in obese patients, hypertensive or arteriosclerotic individuals or those with chronic debilitating or degenerative diseases.

Children are definitely more tolerant to avertin, but nevertheless the same dose scale is used as for adults. If the basal anesthesia is insufficient, however, more supplemental anesthesia should be used rather than an increase in the dose of avertin. Boyd (1935) reported 700 cases without fatality in which avertin was employed as a complete anesthetic in children, in doses of 175 mgm to 200 mgm per kg; but in 2.5 per cent of his patients, stimulation of respiration or circulation was required. The use of avertin for full surgical anesthesia in children should not be countenanced, despite occasional reports of success.

The patient's reflex irritability is of importance in calculating the dose of avertin. For example, each of two patients may be given 80 mgm per kg of the drug. One with low reflex excitability may be asleep within a few minutes, while the other with a high level of reflex excitability remains in a state of restless delirium. If the first patient had received 60 mgm per kg and the second patient 100 mgm, both would be in approximately the same state of basal anesthesia.

Technic. Avertin with amylene hydrate is administered only by rectum. A cleansing enema is given beforehand. The properly prepared avertin solution is allowed to flow gently by gravity (from a height of two feet) through a rectal

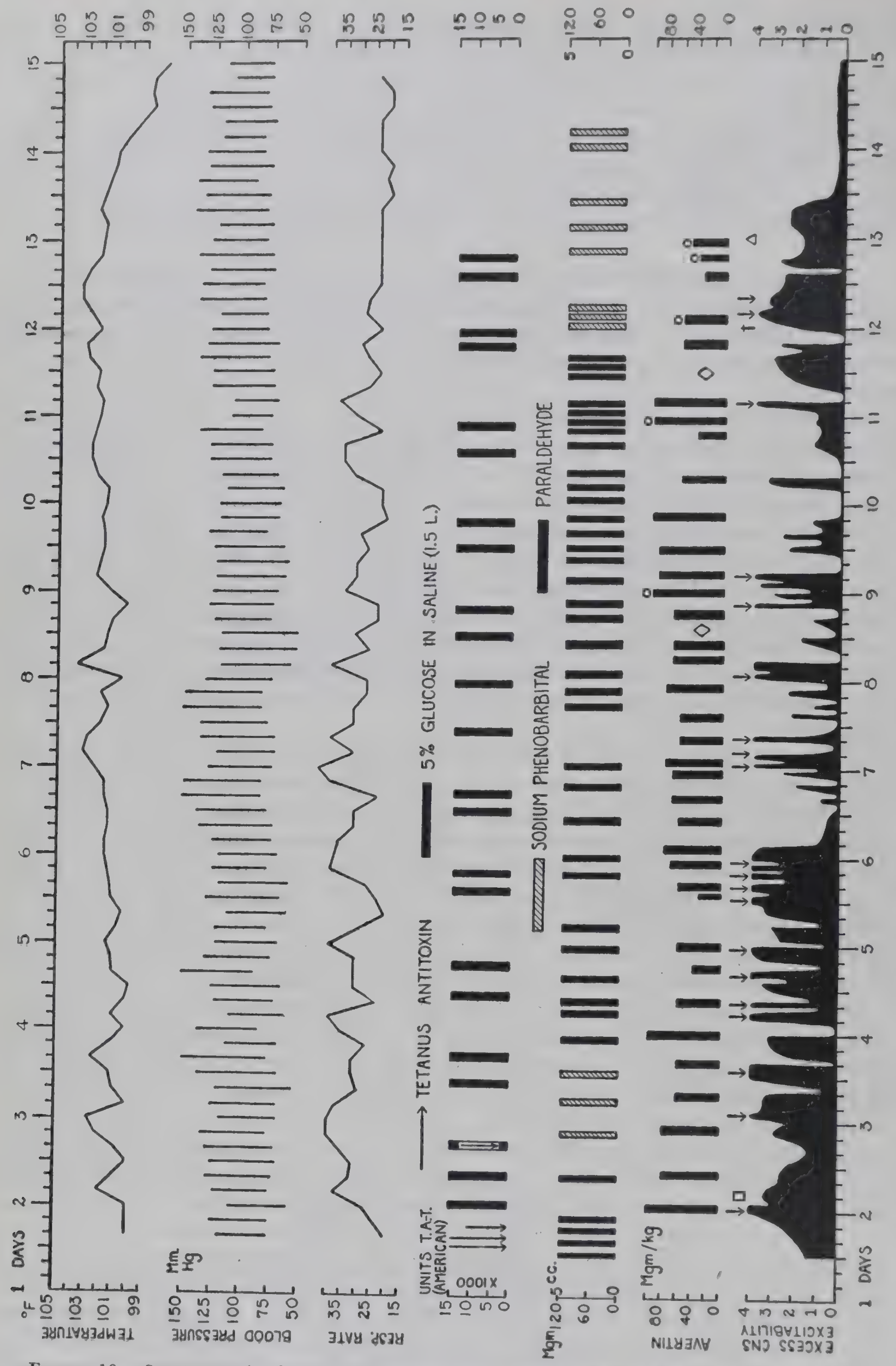

Figure 10. *Symptomatic therapy of tetanus with central nervous system depressants.*

Mechanic, aged 26, weight 82 kg. Patient admitted to hospital three days after sustaining a lacerating wound of the right index finger. Examination showed stiffness of the neck, hyperactive deep reflexes, trismus and spontaneous mild tonic spasms of various muscle groups. Within a few tube introduced into the lowest part of the bowel. The avertin is given 20 minutes or more before operation is contemplated. Fully three to five minutes should be allowed for the administration. High and rapid injection may cause speedy absorption and undue depression of the respiration and blood pressure.

The calculated dose of avertin in amylene hydrate is dissolved in approximately 40 volumes of distilled water or physiological sodium chloride solution, previously heated to exactly 40 C., and shaken vigorously until all globules of avertin liquid have disappeared. Above 40 C., hydrobromic acid and dibromacetaldehyde may be liberated, and these compounds can cause severe injury to the rectal mucous membranes. The avertin with amylene hydrate should go entirely into solution and if crystals of avertin appear, the mixture must be discarded. Congo red solution is supplied with each bottle of avertin, and is used to test the pH of the anesthetic mixture. If the avertin solution is too acid, it must not be used because it is decomposed and dangerous. The anesthetic solution is administered before cooling occurs. Details must be rigidly observed as improper technic may result in severe reactions, such as hemorrhagic proctitis. Diseases of the rectum and sigmoid obviously contraindicate the use of avertin.

Advantages of Avertin as a Basal Anesthetic. Avertin has the advantages of ease of administration and pleasant induction. The mental distress and respiratory irritation incident to the use of several inhalation anesthetics are avoided. Postoperative sequelae are few and the incidence of nausea and vomiting is not high. Basal anesthesia with avertin decreases by one-half the amount of inhalation anesthetic subsequently needed. The resultant depressant effects, however,

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hours, the patient's condition rapidly became worse and three severe generalized convulsive seizures occurred in rapid succession. Patient remained unconscious from the onset of symptomatic therapy with avertin until the eleventh hospital day. Within the first 28 hours, 40,000 units (American) of tetanus antitoxin were injected intramuscularly, and 10,000 units intravenously. Nutrition, body water and electrolytes were maintained purely by means of intravenous infusions of glucose and saline. Body weight fell 14 kg. The attempt was made to control the extreme hyperexcitability of the nervous system by the intramuscular injection of paraldehyde and sodium phenobarbital and the rectal instillation of avertin in amylene hydrate, in amounts and at intervals shown in the figure. The degree of success obtained is depicted in the solid black area at the bottom which indicates, on an arbitrary scale, the degree of excess nervous system excitability. The zero line does not represent normality but rather the absence of convulsive phenomena. Even when the patient was completely anesthetized, motor restlessness and tonic spasms occurred at times.

Observe that paraldehyde and sodium phenobarbital were considerably less effective than tribromethanol in giving symptomatic relief, but even deep anesthesia with avertin did not annul the neuromuscular phenomena characteristic of tetanus. This suggests that tetanus convulsions differ in point of origin from those produced by convulsant drugs (Harvey, 1939). Over a period of 12 days, 38 injections of paraldehyde were given (190 cc), 11 of phenobarbital (1.3 grams), and 36 doses of avertin totalling (exclusive of enemas in part expelled) 2070 mgm per kg or 170 grams.

Despite the large amounts of avertin, urobilinogen tests revealed no liver damage, and bromsulfalein dye excretion tests performed on the 22nd and 29th day resulted in normal figures. The blood pressure and respiratory rate, as well as the temperature, throughout the course of the illness are also shown in the chart. Note that the cardiovascular and respiratory systems were not adversely affected by the large amount of depressant drug medication. (Case data through courtesy of Dr. B. S. Brody, Yale University School of Medicine.)

↓ Each arrow represents a series of severe convulsive seizures characterized by generalized tonic muscular spasm, opisthotonos and cyanosis lasting thiry seconds or more.

° Incomplete retention of avertin enemas.

◇ Urobilinogen tests.

▭ Patient unconscious from this point until 12th day.

† Consciousness regained.

△ Taking food well by mouth.

are probably only additive. The long postanesthetic period of sedation is of special value in cases of brain surgery and severe hyperthyroid disease. It lasts several hours and obviates the need of analgesics and hypnotics.

Special Uses of Avertin as a Basal Anesthetic. In thyrotoxic patients who are extremely nervous and apprehensive, once the written consent of the patient for operation is obtained, avertin can be given without the patient knowing that he is scheduled for surgery. In patients with pulmonary disease, avertin has the advantages that it is not excreted by the lungs and that it greatly reduces the amount of inhalation anesthetic necessary. In cases of brain surgery, inhalation anesthesia generally raises the cerebrospinal fluid pressure. Avertin, on the other hand, tends to lower intracranial pressure, and has been found particularly suitable for neurosurgery. The fall in cerebrospinal fluid pressure noted in animals under avertin anesthesia (Seevers and associates, 1931; Finesinger and Cobb, 1935) agrees with the clinical experience of neurosurgeons using avertin basal anesthesia. For biopsy procedures in patients with questionable malignant growths, avertin removes apprehension by keeping the patient asleep while the frozen sections, pathological examination, diagnosis and consultation are being made. If radical surgery is decided upon, the patient is already under basal anesthesia.

Avertin in Convulsive States. Avertin may at times be effectively employed for the symptomatic therapy of certain convulsive states including tetanus, status epilepticus and eclampsia. It may also be useful in controlling maniacal patients. For the convulsions of tetanus, avertin can be given repeatedly over a period of many hours or several days. As many as 30 doses of 60 to 80 mgm per kg each have been administered to patients for the control of severe convulsions. In one instance, 170 grams were given over a 12 day period. Recovery followed, and no liver damage developed (Figure 10). The dose of the drug is reduced and the interval between doses is increased as improvement occurs.

Disadvantages. The chief disadvantage of avertin is that it is a fixed, nonvolatile anesthetic. The anesthetist therefore lacks adequate control once it is administered. Avertin is a halogenated hydrocarbon and thus has the potentiality for damaging parenchymatous organs. Differences in the rates of absorption and excretion of avertin may cause marked variations in the depth and duration of anesthesia. Avertin is safe only in doses producing basal anesthesia and therefore a second anesthetic agent is required. Experience shows that the toxicity of anesthetic combinations is that of the most toxic member, and this fact demands careful selection of the supplemental agent. Constant nursing is required from start to recovery of avertin anesthesia, and also during the long postanesthetic sleep. Under many circumstances, a prolonged postanesthetic sleep is not desirable. Avertin anesthesia is limited to operations of moderate length, due to the rapid rate of excretion of the drug, and greater increments of supplemental anesthesia must be used if the operation is prolonged.

Contraindications. Addicts to alcohol manifest cross-tolerance to avertin; therefore the basal anesthetic dose is difficult to judge and may need to be so large that injury to parenchymatous organs may result. The presence of hepatitis, cirrhosis, and jaundice usually contraindicates the use of avertin, because of the possibility of further damage to the liver and for the reason that the liver plays an important rôle in the detoxification of the drug. Patients with nephritis should not receive avertin, because the kidney is the obligatory channel of excretion and further renal damage may occur. Although avertin has been used apparently with safety in persons with chronic low-grade renal impairment, acute or severe renal insufficiency is an absolute contraindication. In diseases of the rectum and colon, such as tumors, enteritis, ileus, obstruction, etc., avertin anesthesia should not be used. The drug should not be administered to hypotensive or hypertensive patients unless ephedrine or benzedrine is used to prevent a marked fall in blood pressure. Patients with poor respiratory exchange due to far advanced pulmonary disease should not receive avertin, and it is also wise not to use it for those with severe heart failure, acidosis, toxemia, shock, severe sepsis, anemia and marked hypothyroidism. Although avertin tends to cause uterine atony, it has been employed in the second stage of labor; but even low doses (60 mgm per kg) which cause only analgesia and amnesia may delay labor and make the patient unmanageable. Larger amounts may seriously depress the fetal respiratory mechanism. The drug is not advisable in obstetrics.

Lack of experience with avertin is a final contraindication to its use. Shipway (1935), in discussing his experience with 1600 administrations of avertin, says, "The practitioner who is called upon to administer anesthetics on few and irregular occasions, or is but a beginner at this arduous and hazardous speciality, will be well advised to leave avertin severely alone."

Antagonists. In case the anesthetic action of avertin becomes too profound, pharmacological antagonists may be needed. Treatment consists in the use of agents which stimulate the respiratory and vasomotor centers, lessen the intensity of the anesthesia and raise the blood pressure. Carbon dioxide, ephedrine, picrotoxin, metrazol, and caffeine with sodium benzoate are helpful. If shallow respiration and feeble pulse appear early as an index of overdosage, the washing out of the rectum to remove the unabsorbed avertin is a procedure not to be scorned. Other aids will be found under the discussion of the treatment of barbiturate and morphine poisoning (pages 142, 210).

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CHAPTER 8

THE ALCOHOLS

ETHYL ALCOHOL

Alcoholic beverages have been used since the dawn of history and the opinions and traditions of the past often cloud the discussion of this subject. Alcohol was formerly believed to be a remedy for practically all diseases. This is indicated by the term "whisky" (Gaelic: "usquebaugh," water of life). It is now recognized that the therapeutic value of alcohol is much more limited than is its social value.

Pharmacological Actions

Local. Alcohol injures cells by precipitating and desiccating protoplasm. This results in the shrinkage of tissue and alcohol is thus an astringent. It is also an irritant to denuded skin and to mucosa. The more concentrated the alcohol, the more pronounced are its effects. The use of alcohol for hardening and dehydrating tissues preparatory to histological section provides a familiar instance of the local action of alcohol.

Skin. Alcohol causes cooling of the skin by evaporation. Alcohol sponges are therefore commonly employed in fevers. Alcohol rubbed on the skin produces mild redness and burning, and therefore it is employed as a counter-irritant and rubefacient. It is routinely used in bedridden patients to prevent bedsores and decubitus ulcers, for it hardens and cleans the skin and helps to prevent sweating.

Mucous Membrane. The irritant action of alcohol is marked on mucosae. The use of strong solutions may result in considerable inflammation. For example, chronic gastritis and enteritis are not uncommon in steady drinkers.

Subcutaneous Tissue. Alcohol injected hypodermically causes considerable pain followed by anesthesia. If the injection is made close to nerves, degeneration may occur. Injections in or near nerves are deliberately used to cause anesthesia of protracted or even permanent character in the treatment of severe pain, especially in sciatica or tic douloureux.

Action on Bacteria. The optimal bactericidal concentration of alcohol is 70 per cent *by weight* (Price, 1939). Alcohol in concentrations varying only slightly from this optimal value are definitely less effective. A concentration of alcohol below 60 per cent or above 80 per cent cannot be depended upon to exert any antiseptic action, probably due to the fact that solutions of these strengths do not readily penetrate protein. Indeed, Price found that 70 per cent alcohol by volume is almost useless as a germicide. Inasmuch as alcohol by weight has no constant volume per cent equivalent, Price has described a relatively simple method for preparing a 70 per cent concentration by weight from commercial alcohol. Very high concentrations of alcohol may dehydrate bacteria without killing them.

Systemic Actions

After absorption, alcohol in sufficient amount affects nearly every tissue of the body, but in particular the nervous system.

Central Nervous System. The question whether alcohol is a "stimulant" has long been debated. Laymen in particular view alcoholic drinks as stimulating. It may be stated categorically that alcohol is not a stimulant but rather a primary and continuous depressant of the nervous system. In this respect it shares the characteristic action of the general anesthetics. The apparent stimulation results from the unrestrained activity of lower centers freed by the depression of higher inhibitory control mechanisms. A familiar example of this is seen in the excitement stage of anesthesia.

Psychic Effects. Horace wrote, "What wonders does not wine! It discloses secrets; ratifies and confirms our hopes; thrusts the coward forth to battle; eases the anxious mind of its burden; instructs in arts. Whom has not a cheerful glass made eloquent! Whom not quite free and easy from pinching poverty!"

The psychic phenomena which follow the ingestion of alcohol arise from an inhibition or depression of higher mental processes, especially those depending on training and previous experience and which usually make for sobriety and self-restraint. The finer grades of discrimination, memory, concentration and insight are dulled and then lost. Impulsive speech and actions result, and inhibitions are removed. Confidence abounds, the personality becomes expansive and vivacious, and speech may become eloquent and occasionally brilliant. Mood swings are uncontrolled and emotional outbursts frequent. The individual may believe himself powerful enough to whip several strong men even when it takes this number to hold him upon his feet. The particular type of behavior manifested under the influence of alcohol is the resultant of three factors,—the personality of the individual, tolerance for the drug, and extraneous stimuli including those provided by the presence of others. Drinking is usually done in company and much of the hilarity, joviality and excitement is dependent upon mutual stimulation.

Carefully performed experiments have shown that alcohol increases neither the mental nor physical abilities. Although the individual estimates his own performance as greatly improved, in reality actual measurement shows it to be inferior. The tests have been concerned with typewriting, target practice, etc., as well as with complicated mental problems, and all the results indicate decreased efficiency. Familiar and habitual tasks, especially if mechanical in nature, are less markedly affected than is work requiring skill, thought and attention.

Brain and Cord. Alcohol is an irregularly descending depressant of the central nervous system. General anesthesia from alcohol lasts much longer than that from chloroform or ether, due to the slow oxidation and delayed excretion of alcohol. Alcohol differs from the volatile anesthetics in that over 90 per cent of it is destroyed in the body. There is little margin between the anesthetic and fatal doses. For these reasons, alcohol is not employed as a general anesthetic.

As an anesthetic, alcohol occupies a place between the general anesthetics and the hypnotics. It is still occasionally used as an analgesic and hypnotic, but much more so by the laity than by the medical profession.

Respiration. There is no clear evidence that the respiratory center is stimulated by ordinary doses of alcohol. Depression of respiration does not occur, however, except late in the course of marked alcoholic intoxication. Respiratory effects from clinical doses of alcohol are negligible and ancertain.

Cardiovascular System. The blood pressure does not change significantly after moderate amounts of alcohol. The pulse rate may increase, but this is usually secondary to muscular activity. The cardiac effects are slight and inconstant, and difficult to attribute to alcohol. Any claim that the force of the heart beat is increased by alcohol is certainly not proved. High concentrations of alcohol depress the heart, but this toxic action is less marked than with chloroform or ether. For example, the beat of the excised mammalian heart is stopped within two minutes when the organ is perfused with 0.15 per cent chloroform, but is not noticeably affected by two per cent alcohol. Much lower concentrations of alcohol (0.10 to 0.30 per cent), however, definitely decrease the total energy output of the heart (Peters and associates, 1936). Central vasomotor factors undoubtedly contribute to the cardiovascular depression in late alcohol poisoning.

Alcohol causes vasodilatation, especially of the cutaneous vessels, and produces a warm and flushed skin. Vasodilatation may be a central vasomotor effect because the direct action of alcohol on vessels is insignificant. The vasodilatation produced by alcohol is utilized in the treatment of certain peripheral vascular diseases. Most cardiologists agree that the coronary arteries are dilated by moderate doses of alcohol and that alcohol is not an etiological factor in angina pectoris (White and Sharker, 1934). Some consider alcohol to be the best drug in the treatment of angina pectoris. The "quieting effect" of alcohol on the pulse of patients with fever results from a central depressant rather than from a peripheral cardiac action.

Body Temperature. Although one feels warm after ingestion of alcohol, due to the increased cutaneous and gastric blood flow, heat loss increases and internal temperature falls. Increased sweating may occur and enhance the heat loss. Only with large amounts does the fall in body temperature become pronounced and this effect is then also due to the depression of the central mechanism which regulates temperature. The action of alcohol in lowering body temperature is naturally greater when the environmental temperature is low, or when the mechanism dissipating heat is disturbed, as during fever. The taking of alcoholic beverages to "keep warm" in cold weather is obviously irrational, and may be dangerous if the conservation of body heat is essential. Those experienced in polar exploration are well acquainted with these facts.

Gastro-intestinal Tract. The effects of varying concentrations and types of alcoholic beverages on the gastro-intestinal motor and secretory functions are influenced by a number of factors. Among these are the state of the digestive processes, the presence or absence of gastro-intestinal disease, the amount and type of food present, the degree of tolerance for alcohol, accompanying psychological factors, etc. Salivary secretion is usually stimulated reflexly by alcohol. If the individual likes alcohol, a secretion of appetite juice rich in acid will ensue. The presence in the stomach of alcohol in concentrations of approximately 10 per cent results in a gastric secretion rich in acid but poor in pepsin. An alcohol meal is thus employed as a functional test for the ability of the gastric glands to secrete free hydrochloric acid. Although pepsin is decreased in amount, peptic digestion is not interfered with by low concentrations of alcohol. Also gastric motility is not impaired. Alcohol stimulates gastric secretion by a reflex action. When it is placed in the stomach of a Pavlov pouch dog, the gastric pouch manifests typical secretory activity.

As the concentration of alcohol in ingested beverages is elevated approximately to 20 per cent and above, secretion tends to be inhibited and peptic activity is depressed. Malt liquors and wines, even in lower concentration, cause a similar inhibition. This is due mainly to the colloidal substances, tannins and organic acids which they contain rather than to their content of alcohol. Strong alcoholic drinks of 40 per cent strength and over are quite irritating to the mucosa and cause congestive hyperemia and inflammation. The presence of food tends to decrease the concentration of alcohol and lessen irritation, and the stomach itself secretes protective mucus. The long-continued use of strong alcoholic beverages may result in chronic gastritis. Achlorhydria is common in chronic alcoholism. A small amount of concentrated alcohol may act as a carminative.

Alcohol apparently has little deleterious effect on the intestinal or pancreatic secretions. Intestinal digestion is not likely to be impaired and the secretion of pancreatic juice may be stimulated by small doses of alcohol. Alcohol which reaches the intestine is diluted by gastric secretions and mucus. No one contends that the use of *large* amounts of alcohol is without serious effects on gastro-intestinal function. The crucial problem centers about the use of moderate amounts of alcoholic drinks. If one enjoys alcohol, small amounts cannot be considered deleterious, and may affect digestion favorably if taken with meals. The influence of alcohol on the digestive tract has been extensively reviewed by Beazell and Ivy (1940).

Kidney. Alcohol increases the flow of urine. This is caused not by any potent diuretic action of alcohol but rather by the large amounts of fluid ordinarily ingested while drinking alcoholic beverages.

High concentrations of alcohol may injure the renal epithelium, especially if there is pre-existing kidney damage, although this point is disputed. It is difficult to attribute to alcohol alone the renal disease occurring in addicts. It has been stated, however, that the kidneys of habitual drinkers are not normal. Most pathologists disagree with the implications of this statement and there is considerable evidence to show that the incidence of nephritis is not exceptionally high in addicts, and that alcohol does not further damage the kidney in patients with Bright's disease. The experiments of Bruger, Localio and Guthrie (1939) are significant in this connection. They performed Addis counts, urea clearances and careful blood and urine studies in normal subjects, in patients with acute and chronic diffuse nephritis, and in patients with arteriosclerotic nephritis before and after the ingestion of varying amounts of alcohol or whisky. In patients with acute or chronic nephritis, proteinuria was rarely augmented; the number of red blood cells and casts in the urine was not increased and renal function was not changed. In subjects with arteriosclerotic nephritis, however, a transient increase in the Addis count and temporary decrease in renal function were caused by alcohol. In normal persons, whisky or alcohol had no deleterious effects on the kidneys. The effects of alcohol on the normal and pathological kidney have been reviewed by Bruger (1940).

Sexual Functions. It is a popular notion that alcohol is an aphrodisiac. Shakespeare, however, realized that inebriation interfered with coitus. In Macbeth, for example, the following conversation occurs (Act 2, scene 3):

Macduff: What three things does drink especially provoke?
Porter: Marry, sir, nose-painting, sleep, and urine. Lechery, sir, it provokes, and unprovokes; it provokes the desire, but it takes away the performance. . . .

Loss of inhibition and restraint is the cause of the sexual behavior seen after alcohol.

Skeletal Muscle. Alcohol is not a true stimulant of muscular activity. From some experiments, it would appear that the total amount of work accomplished may be increased under the influence of small doses of alcohol but this is largely due to a lessened appreciation of fatigue. Alcohol is also a readily available source of energy for muscular work. Furthermore, vasodilatation may improve the circulation in muscle. There is little reason to believe, therefore, that alcohol has any direct effect on muscle contractility. Large doses of alcohol decrease the amount of muscular work accomplished. This is due to the central nervous system depression. The opinion that moderate doses of alcohol directly depress muscle is unsupported by acceptable evidence.

Absorption, Fate and Excretion of Alcohol. *Absorption.* Alcohol is rapidly absorbed from both the stomach and intestine. The stomach usually absorbs about 20 per cent of the ingested alcohol and the intestinal tract the remainder. Most of the alcohol gains entrance to the body through the jejunum and absorption is usually completed in two and one-half hours. The rate of absorption varies directly with the concentration. It is well known that alcohol taken as whisky is more readily absorbed than the same amount taken as beer. Many factors may retard gastro-intestinal absorption of alcohol. That food is a most important factor is obvious from the difference in effects obtained by drinking a cocktail before dinner as contrasted with its effects when taken after dinner. Experienced drinkers therefore take food with their drinks.

Absorption of alcohol occurs readily through the colon. Vaporized alcohol can be absorbed through the lungs. Intoxication and even death may ensue from the inhalation of alcohol. Subcutaneous absorption is also rapid, if the concentration of alcohol is not too high. It is doubtful whether absorption occurs through the skin.

Distribution. Alcohol differs from most foods in that it is unchanged in the intestines and is absorbed as such. All organs and fluids of the body contain alcohol within a few minutes after it is ingested. It also gains ready access to the fetal circulation. The distribution of alcohol in various tissues is fairly uniform. However, the concentration of alcohol in the brain and spinal fluid is slower in rising and falling than that in other tissues. A similar delay in equilibration occurs in the case of bromide. The amount of alcohol found in the brains of patients dying of alcoholic intoxication varied from 0.27 to 0.51 per cent (Gettler and Tiber, 1927).

Oxidation. Ninety to 99 per cent of alcohol is almost completely burned in the body. In the process of oxidation, energy is released and carbon dioxide and water are produced. The rate of oxidation is thought to be fairly constant regardless of the amount of alcohol present in the tissues, at least as measured by the rate of its disappearance from the blood. For example, if the amount of ingested alcohol is increased 100 per cent, the rate of disappearance of alcohol from the blood is accelerated by only 17 per cent (Newman and coworkers, 1937). When large amounts of alcohol are given, oxidation may be incomplete and aldehydes, acetic acid and other substances are thought to be formed as intermediary products. These may appear in the breath and urine. Haggard, Greenberg and Cohen (1938) suggest from their experiments that the rate and completeness of oxidation of alcohol vary with different types of beverages. For example, two whiskies with equal alcoholic content may require widely varying periods for oxidation. The nature of the substances which account for this phenomenon is undetermined.

The amount of alcohol oxidized per unit of time varies somewhat with the individual. Studies on man (Higgins, 1917) indicate that approximately 3.5 cc of alcohol are burned per hour. At this rate approximately eight hours would be required for the oxidation of one ounce of alcohol. However, on the basis of experiments on dogs, Mellanby (1919) calculates that a man of average weight can burn about 10 cc of alcohol per hour. Other figures vary from six to 15 cc per hour. Atwater and Benedict (1902) concluded that 90 cc of alcohol taken in the form of six ounces of whisky require approximately six hours for oxidation. The rate of combustion in persons habituated to alcohol as compared to that in occasional drinkers is not known, although it appears to be the same despite the fact that the blood level falls faster in the former group. If the rate of combustion of alcohol in man is accepted as 10 cc per hour (approximately eight grams), 56 calories per hour can be supplied in this manner.

The liver is probably the chief site of the initial oxidation of alcohol, and insulin appears to be necessary for this function. Clark and coworkers (1939) have shown that depancreatized dogs and cats receiving no insulin oxidize alcohol at a rate very much below normal. Also, hepatectomized animals oxidize alcohol at a rate comparable to that in the depancreatized preparations, and injections of glucose and insulin did not hasten the rate of disappearance of alcohol. Thus oxidation of alcohol in the liver under the influence of insulin is strongly suggested. Indeed, the investigations of Goldfarb, Bowman and Parker (1939) support the view that there is a definite relation between the oxidation of alcohol and the oxidation of glucose. They studied a series of alcoholic patients with a history of drinking and presenting various degrees of intoxication. The subjects were classified in four groups and managed as follows: (1) no therapy; (2) subcutaneous injection of 15 units of insulin; (3) intravenous administration of 50 cc of 50 per cent glucose; (4) simultaneous administration of insulin and glucose in the above doses. The blood alcohol levels were then followed and the rapidity of the emergence from intoxication noted. Insulin therapy alone had no effect on the disappearance of alcohol from the blood. Glucose alone hastened the reduction in blood alcohol levels only in the more severely intoxicated patients. Therapy with glucose plus insulin accelerated recovery in both moderately and severely intoxicated patients. Consciousness was regained within one and one-half to two hours, at which time a rational history was usually obtainable, and some subjects showed adequate motor co-ordination within four to five hours. Goldfarb, Bowman and Parker suggest that the oxidation of alcohol may be catalyzed by the simultaneous oxidation of glucose. This treatment of acute alcoholism appears promising, and the immediate attendance of the physician is required for only a brief time (Figure 11).

Excretion. Normally, about two per cent of ingested alcohol escapes oxidation and is excreted. Under special circumstances and when large doses have been consumed, this figure may be as high as 10 per cent. Alcohol leaves the body mainly through the kidneys and lungs, but it can also be detected in sweat, tears and other secretions.

The amount of alcohol eliminated through the lungs ordinarily is less than 0.5 per cent and rarely exceeds two per cent of that ingested. The "strong" odor imparted to the breath is mainly due to other volatile constituents of the beverage. The concentration of alcohol in the expired air parallels at a much lower level that in the blood and has been used extensively as an index of the amount of alcohol in the blood and tissues. An intoxicated person may excrete several milligrams of alcohol per liter of air, and one gram per hour may escape in this way if respiratory minute volume is increased by excitement, exercise or inhalation of carbon dioxide. Hyperpnea induced by carbon dioxide has been used to hasten excretion by the lungs and bring patients out of alcoholic coma, but it is doubtful whether recovery is hastened by the slight additional excretion of alcohol.

The concentration of alcohol in the urine also varies with that in the blood.

The urine of an intoxicated person may contain as much as five grams per liter. The total renal excretion of alcohol, however, rarely exceeds three per cent of that ingested, and within eight hours as a rule the urine is free of alcohol. Some reabsorption of alcohol occurs from the bladder epithelium when the urine concentration is much higher than that of the blood. Alcohol is one of the few substances which the normal bladder mucosa can absorb.

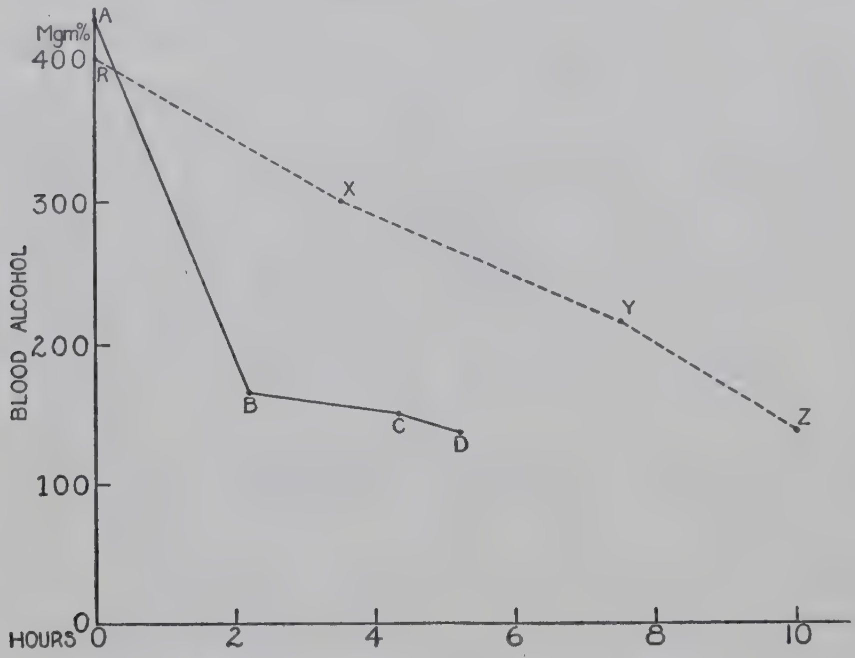

FIGURE 11. *The effect of glucose and insulin on the recovery from acute alcoholic intoxication.*

Two patients, both chronic drinkers, suffering from acute alcoholic intoxication with blood alcohol levels approximately 400 mgm per cent at the time of admission to the hospital. *Solid line,* blood alcohol curve of patient who at zero time was given an intravenous injection of 50 cc of a 50 per cent solution of glucose and 15 units of insulin. *Broken line,* blood alcohol curve of patient receiving no treatment. At *A;* the treated patient could not be awakened but groaned and struggled in response to stimulation; at *B,* he was aroused by the stimulus of a venepuncture and was oriented and clear; at *C,* he was awake, oriented and mentally clear; at *D,* he requested discharge and was able to walk without difficulty. At *R,* the untreated patient was comatose and did not respond readily to stimuli; at *X,* he was aroused by the stimulus of a venepuncture but dysarthria, confusion and disorientation were prominent; at *Y,* the patient was awake but flushed and nauseated, and he was not well oriented until the tenth hour (*Z*). It is clear that glucose and insulin therapy causes a rapid fall in the concentration of blood alcohol and results in clinical recovery at a time when the untreated patient is still intoxicated. Note that chronic drinkers are well oriented at blood alcohol levels which would be associated with drunkenness in the occasional drinker. (Drawn from case data supplied through the courtesy of Dr. Walter Goldfarb.)

Much attention has been given to the relation between the urine and blood levels of alcohol. It has been contended that the urine concentration is the same, for practical purposes, as the blood concentration and that differences may be accounted for on the basis of time elapsed in urine formation and excretion. It is difficult to reconcile this belief with the modern concept of the mechanism of urine formation unless it is assumed that alcohol and water are reabsorbed in the same proportion by the renal tubule. Others contend that the blood values are uniformly and significantly lower than those of the urine (Miles, 1922). Southgate and Carter (1926) found the urine: blood ratio to be 1.35:1.0. The urinary alcohol levels can be used to indicate the blood and tissue concentration (Table 3).

Only traces of alcohol are found in the other secretions of the body. There is no evidence, for example, for the belief that nursing infants can become intoxicated from alcohol ingested by the mother. Also, the amount and quality of the milk are undisturbed by the taking of alcohol in moderation by the nursing mother. Traces of alcohol are found in the bile, but are apparently reabsorbed by the intestine.

Concentration of Alcohol in the Blood and Its Relation to Alcoholic Intoxication. Within five minutes after its ingestion, alcohol can be detected in appreciable amounts in the blood. It is carried especially in the plasma which is said to contain twice as much as the corpuscles. Inasmuch as alcohol is absorbed rapidly and oxidized slowly, it accumulates in the blood and tissues. After a single administration, the highest blood level is reached between the first and second hour and from then on it falls slowly, depending on the rate of oxidation, the degree of excretion, the amount remaining to be absorbed in the intestinal tract, and the presence or absence of tolerance.

The curve of blood alcohol concentration of the abstainer differs from that of the habitual drinker. In the former, the blood concentration remains high for several hours, whereas in the habitué the peak level is reached more quickly and is lower, and the curve descends rapidly after two hours. The character of the curve also depends on the concentration of ingested alcohol. Miles (1924) gave 27.5 grams of alcohol in two dilutions, in one case diluted with water to 1000 cc and in the other to 100 cc. In the first instance, the concentration in the venous blood was lower and slight symptoms or none were noted, whereas with the stronger drink higher levels and definite symptoms were observed. These results are summarized in Table 3.

TABLE 3

ALCOHOL CONTENT OF THE BLOOD AND URINE AFTER TAKING 27.5 GRAMS IN DIFFERENT SOLUTIONS *

(Miles, 1924.)

	ALCOHOL IN MGM PER CC AFTER 27.5 GRAMS IN 1000 CC				ALCOHOL IN MGM PER CC AFTER 27.5 GRAMS IN 100 CC			
Time (minutes)	20	40	70	120	20	40	70	120
Blood conc. **	.18	.24	.31	.31	.29	.43	.44	.37
Urine conc.	.16	.38	.48	.43	.26	.54	.63	.50

* Average of nine subjects.
** Blood samples taken two minutes after urine samples.

The blood level of alcohol which indicates intoxication or drunkenness is a matter of dispute. Generally, however, it is agreed that an alcohol concentration of 0.20 per cent (200 mgm per cent) either in the blood or urine is associated with mild to moderate intoxication. This has been called the "crucial concentration." In some persons, of course, this level does not indicate drunkenness, and it must be viewed merely as an average. In the same sense, a blood level of 0.25 per cent usually signifies moderate to marked intoxication. Over 90 per cent of persons with concentrations of blood alcohol of 0.30 per cent are obviously intoxicated.

Jetter (1938) studied 1150 cases hospitalized with preadmission diagnoses of acute alcoholism. In 1000 of these cases, the blood alcohol was determined and in 80 per cent ranged between 0.15 and 0.30 per cent. In 70 per cent of the 381 urine examinations, the concentration of alcohol varied from 0.20 to 0.35 per cent. The incidence of clinical intoxication found at different levels of blood alcohol is shown in Table 4.

TABLE 4

RELATIONSHIP BETWEEN INCIDENCE OF CLINICAL INTOXICATION AND LEVELS OF BLOOD ALCOHOL

(Jetter, 1938).

Blood Alcohol Concentration	0.05 %	0.10 %	0.15 %	0.20 %	0.25 %	0.30 %	0.35 %	0.40 %	0.45 %	0.50 %
Total Number of Cases	38	87	132	330	176	141	74	15	5	2
Number of Cases Intoxicated	4	16	61	276	158	133	71	14	5	2
Percentage of Cases Intoxicated	10.5	18.4	47.0	83.6	90.0	95.1	96.0	93.3	100	100

A blood alcohol value of 0.40 per cent always indicates advanced drunkenness. The fatal concentration lies between 0.50 and 0.80 per cent. Blood concentrations of alcohol below 0.20 per cent are often associated with unequivocal clinical evidences of intoxication. For example, with values around 0.06 per cent most people manifest definitely decreased competence; with levels of 0.10 per cent, about one-quarter of a group of individuals would be classified as intoxicated. As this level rises to 0.15 per cent, one-half would be considered clinically intoxicated. Inasmuch as expired air or urine may be more easily obtained than blood from an intoxicated person, the level usually set in medico-legal work for drunkenness is a urinary alcohol level of 0.20 per cent or a concentration of alcohol in exhaled air of 1.0 mgm per liter.

The amount of alcohol which must be ingested to cause given blood concentrations of alcohol varies from person to person and depends on many factors. In general, it may be assumed that for every 0.01 per cent of alcohol in the blood, from five to 10 cc of alcohol were ingested. On the basis of the latter figure, this is the equivalent of about 200 cc of beer (4.5 per cent alcohol by volume) or 25 cc of whisky. Also on this basis, drunkenness would usually be produced by 150 cc of alcohol, one pint of whisky or about seven average bottles of beer. When six to eight cc of alcohol per kg of body weight are rapidly absorbed, death usually occurs. This holds true for nearly all species of mammals. The quantitative differences in the effects of gin, whisky and beer on the blood alcohol levels of normal persons and the influence of the time of ingestion in relation to meals have been analyzed by Haggard and associates (1938).

In the following table are given the symptoms which ordinarily appear at different levels of ascending concentrations of blood alcohol in persons with ordinary sensitivity, as compiled by Miles (1932). It is of interest that for equal concentrations of alcohol in the blood, the effects are greater when the concentration is rising than when it is falling.

A SCALE OF TOXIC SYMPTOMS

(Miles, 1932)

Per cent alcohol in blood	Subjective state and observable changes in behavior under conditions of heavy social drinking.
0.010	Clearing of the head. Freer breathing through nasal passages. Mild tingling of mucous membranes of the mouth and throat.
0.020	Slight fullness and mild throbbing at back of head. Touch of dizziness. Sense of warmth and general physical well-being. Small bodily aches and fatigue relieved. Not fretful about the weather nor worried concerning personal appearance. Quite willing to talk with associates. Feeling tone of pleasantness.

0.030	Mild euphoria, "everything is all right," "very glad I came," "we will always be friends," "sure I will loan you some money," "it isn't time to go home yet!" No sense of worry. Feelings of playing a very superior game. Time passes quickly.
0.040	Lots of energy for the things he wants to do. Talks much and rather loudly. Hands tremble slightly, reaching and other movements a bit clumsy; laughs loudly at minor jokes; unembarrassed by mishaps, "you don't think I'm drunk do you, why I haven't taken anything yet." Makes glib or flippant remarks. Memories appear rich and vivid.
0.050	Sitting on top of the world, "a free human being," normal inhibitions practically cut off, takes personal and social liberties of all sorts as impulse prompts. Is long-winded and enlarges on his past exploits. "Can lick anybody in the country," but has observable difficulty in lighting a match. Marked blunting of self-criticism.
0.070	Feelings of remoteness. Odd sensations on rubbing the hands together, or on touching the face. Rapid strong pulse and breathing. Amused at his own clumsiness or rather at what he takes to be the perversity of things about him. Asks others to do things for him. Upsets chair on rising.
0.100	Staggers very perceptibly. Talks to himself. Has difficulty in finding and putting on his overcoat. Fumbles long with the keys in unlocking and starting his car. Feels drowsy, sings loudly, complains that others don't keep on their side of the road.
0.200	Needs help to walk or undress. Easily angered. Shouts, groans, and weeps by turns. Is nauseated and has poor control of urination. Cannot recall with whom he spent the evening.
0.300	In a stuporous condition, very heavy breathing, sleeping and vomiting by turns. No comprehension of language. Strikes wildly at the person who tries to aid him.
0.400	Deep anesthesia, may be fatal.

Tolerance to Alcohol. The repeated use of alcohol results in the development of tolerance, and larger doses must then be taken in order to procure characteristic effects. This tolerance nevertheless is not as marked as for morphine or nicotine. The alcoholic addict still has his upper limit of tolerance and this is usually only two to four times the amount of alcohol that can be taken by the occasional drinker.

The mechanism of tolerance is not clearly understood. Some claim that it is not a true tissue tolerance but rather that it is due to a more rapid rate of oxidation of alcohol in the addicted person. Others believe that retarded absorption is the cause. The work of Newman and Lehman (1938) on dogs and rats indicates that a real tissue tolerance for alcohol develops in habituated animals and that drunkenness appears only when a higher blood level of alcohol is reached than in the controls. They also showed that this acquired tolerance was not due to a decrease in brain permeability to alcohol and that the cells of the central nervous system acquire the ability to function more effectively at a given concentration of alcohol than before habituation occurred. Should this prove true for man, our ideas concerning the concentration of alcohol in the tissues as an index to intoxication would need to be altered. At present, those who disagree with the cellular tolerance theory claim that the chronic drinker becomes intoxicated when his tissue alcohol reaches the same level that produces intoxication in the abstainer, regardless of the actual amount of alcohol ingested. Finally, there is the belief that more alcohol is excreted by the tolerant individual.

Cross-tolerance to the closely allied hydrocarbon anesthetics is also exhibited by alcoholics. For example, it is difficult to anesthetize chronic alcoholics with chloroform, ether, or avertin.

Addiction to alcohol also occurs. However, an individual may be tolerant to alcohol and yet not manifest serious or pathognomonic withdrawal symptoms. In this respect, tolerance to alcohol differs from that to morphine in that the latter is rarely seen without accompanying addiction.

Alcohol as a Food. The combustion of alcohol begins within five or ten minutes after it is swallowed. Hence alcohol is utilized more rapidly than most foods. The energy released per gram of alcohol is approximately seven calories. This energy is available for body work. Alcohol spares carbohydrates and fats and increases glycogen and fat deposition because it cannot be stored in the body or utilized in tissue formation and can only be burned for its energy content. When the diet is deficient in carbohydrate, alcohol can spare protein but not quite as efficiently as can carbohydrate. Alcoholic beverages often contain other foodstuffs. For example, beer contains about 500 calories per quart, half of which are furnished by albuminous and carbohydrate substances.

Considerable controversy exists concerning the classification of alcohol as a food (Emerson, 1932). Alcohol differs from ordinary foods in several distinct ways. It can only be burned and cannot enter into the building of tissue. It is oxidized at a constant rate regardless of supply. Alcoholic beverages often contain no vitamins or accessory food factors, and alcoholic addicts are subject to vitamin deficiency (page 1249). Alcohol has definite pharmacological and toxicological properties not possessed by foods. Finally, taken over a long period of time, alcohol may cause severe organic and mental ailments.

Metabolic Actions. Depression and sleep which follow ingestion of large amounts of alcohol may lower the *energy production* of the body. The reverse is true during the excitement stage of alcoholic intoxication. *Nitrogen metabolism* is undisturbed by alcohol, with the exception of purine metabolism. *Uric acid elimination* is said to be increased, but the mechanism is unknown. The etiologic relation of alcohol to *gout* is not clear. Beer, a chief offender, contains purine substances. In the fully developed case of gout, alcohol appears to precipitate acute attacks but clinical reports differ in this regard.

Resistance to Disease and Infection. A very large amount of clinical and experimental work has failed to indicate that alcohol in therapeutic or moderate amounts has any *direct* effect on man's susceptibility or resistance to disease or infection. Alcohol neither increases susceptibility to tuberculosis, pneumonia or any other disease, nor does it offer any protection. Alcohol may interfere indirectly with the defensive mechanisms, but this is usually by impairment of general health. Thus, an alcoholic addict may stand less chance of recovery from disease. Rosenthal (1930) found that although moderate doses of alcohol in dogs caused only slight impairment of liver function, nevertheless the organ was more prone to damage by hepatotoxic agents. For example, chloroform given to these dogs following recovery from the alcohol caused the death of many of them. When the same amount of chloroform was given before the alcohol, no such lethal outcome was noted. The reader interested in this problem is referred to the discussion by Langmead and Hunt (1932).

Heredity and Longevity. The bulk of animal experiments appears to indicate that the prolonged daily feeding of moderate amounts of alcohol does not interfere with normal growth, maturation, or ability to reproduce. Whether larger doses cause lessened fertility, higher prenatal or early postnatal mortality, and impairment of the offspring is difficult to decide. Davenport (1932) concludes, "There is much evidence that generations of alcoholism in man have produced gametes relatively resistant to alcohol; so that diminished fertility of alcoholics and defective offspring of alcoholics are, at least, not the common result." Stockard (1932) concludes from his animal experimentation, "With full appreciation of all the difficulties in transferring the results obtained from the study of one animal kind to another, we may assume from the experiments on the effects of alcohol in development and inheritance that it is highly improbable that the quality of human stock has been at all injured or adversely modified by the long use of alcohol." The statements regarding the inheritance of proclivity for alcohol, and the high incidence of mental defects, insanity or epilepsy in offspring of alcoholic parents must certainly be critically analyzed. Most of these conclusions are from statistical analyses and the latter are notoriously susceptible to manipulation by biased persons. The children of thousands of drunkards were found the equal of other children. While it is true that children may inherit the defects (insanity, mental deficiency, etc.) which caused alcoholism in the parent, they do not inherit the alcoholism itself.

Actuarial statistics show that heavy drinkers have a shorter span of existence than do abstainers. Whether the prolonged use of moderate amounts of alcohol similarly shortens life, however, is an entirely different problem. Animal experiments tend to show the innocuousness of small amounts in regard to length of life. Pearl (1926) made an extensive study of over 5000 persons in Baltimore whose family records extended over several generations. His conclusions indicate that moderate drinking of alcohol does not shorten life but may actually enhance life expectancy above that of abstainers. Heavy drinkers showed a decreased life expectancy. Despite the numerous objections raised to Pearl's work, it accords with the general trend of clinical opinion that moderate amounts of alcohol may be taken daily with no demonstrable injurious effect. This amount is certainly less than that which causes clinical intoxication. The question is one of the wise use of alcohol as compared to its abuse.

In closing his book on the longevity problem, Pearl (1926) quotes the following humorous pronouncement of Henry Arthur Jones (*The English Review,* December, 1924): "With respect to alcoholic disease, as with other diseases, the chief thing is to get oneself born with an immunity to it. I took this precaution against alcohol, and thereby have been able to enjoy a bottle of wine a day without ever getting drunk, without ever approaching drunkenness, without ever wishing to take more than was good for me. Such are the advantages of belonging to God's elect, as the apostle affectionately calls us. . . . As one born with a joyous capacity for taking a moderate, harmless quantity of wine, I strenuously protest being degraded into equality with C_3 degenerates to whom alcohol is poison. Of all the devastating applications of the false and abominable doctrine of equality, this is one of the most intolerable. Why should a poor but healthy labouring man, whose rich brawny thews and vigorous stomach righteously demand a draught of refreshing ale, be condemned to meagre and gloomy equality with the rich valetudinarian, to whose queasy digestion a mere sip of alcohol is veritable poison? Away with this damnable doctrine of equality when it tells so hardly upon the working man!"

Pathological Effects. This subject can be only briefly reviewed here. Definite histological changes in tissues occur only with the prolonged use of large amounts of alcohol. Even in these cases, it cannot be said with certainty that the alterations are due to the alcohol, because identical changes may occur in abstainers. The nervous system and the digestive system are most markedly affected. In the former, structural changes due to alcohol can rarely be recognized. Polyneuritis and alcoholic pellagra are known not to be due to alcohol and can be cured by proper therapy without removing alcohol from the diet (page 1249). Chronic gastritis and achlorhydria may be seen in heavy drinkers. The so-called alcoholic cirrhosis of the liver is encountered in those who drink spiritous liquors rather than light beverages, but the problem of etiology is unsettled. Animal experiments with alcohol alone are negative as regards cirrhosis and reports on human autopsy series vary. It is certain that a similar cirrhosis can be seen in abstainers. The possible etiological rôle of the copper present in certain alcoholic drinks has been emphasized by some, especially Mallory (page 1119). The relation of alcohol to cirrhosis of the liver has been reviewed by Connor (1940). The kidneys are not greatly affected by alcohol. There is no evidence that alcohol is directly responsible for serious organic heart disease. The studies of White and Sharker (1934) indicate that the use of alcohol bears no relation to the incidence of angina pectoris. Many toxic effects previously attributed to alcohol may be due to impurities in the beverages consumed. The use of methyl alcohol as an adulterant provides a familiar example. The possibility that higher alcohols and aldehydes of "raw" whiskies may cause damage must not be overlooked. This subject has been reviewed by Martland (1932).

Preparations. Alcohol, whisky and brandy are official preparations. *Alcohol* (Ethyl Alcohol), U.S.P., B.P., contains not less than 92.3 per cent by weight (94.9 per cent by volume) of C_2H_5OH. Its appearance and chemical properties need not be described here. *Dehydrated Alcohol,* ("Absolute Alcohol"), U.S.P., B.P., contains not less than 99 per cent by weight of C_2H_5OH. *Diluted Alcohol,* U.S.P., is a mixture of alcohol and water, containing not less than 48.4 per cent and not more than 49.5 per cent by volume of C_2H_5OH. The B.P. includes a series of diluted alcohols ranging from 20 to 90 per cent of C_2H_5OH by volume. *Whisky* (Spiritus Frumenti), U.S.P., is an alcoholic liquid obtained by the distillation of the fermented mash of wholly or partly malted cereal grains, and contains not less than 47 per cent and not more than 53 per cent by volume of C_2H_5OH. It must have been stored in charred wood containers for a period of not less than four years. It is a pale to deep amber-colored fluid with a characteristic odor and taste. *Brandy* (Spiritus Vini Vitis), U.S.P., is an alcoholic liquid obtained by the distillation of the fermented juice of sound ripe grapes, and contains not less than 48 per cent and not more than 54 per cent by volume of C_2H_5OH. It must have been stored in wood containers for a period of not less than four years. It is a pale amber-colored fluid with a characteristic odor and taste.

In addition to official preparations of alcohol, numerous alcoholic beverages are commercially available throughout the world, including various types of gin, wine, liqueurs, ale and beer. Alcohol is also a main constituent of several classes of vehicles (page 1321).

Therapeutic Uses of Alcohol. Alcohol and alcoholic beverages are used widely by the laity for a large number of ailments and the proper delimitation of its legitimate uses in medicine is sometimes difficult.

External. Alcohol is an excellent *solvent* for many drugs, and is frequently employed in *medicinal mixtures* as a vehicle. Alcohol is a solvent for the *toxicodendrol* causing ivy poisoning; early and thorough washing of the affected parts with alcohol may abort or lessen the severity of this dermatitis. Alcohol (25 per cent) *cools* the skin when allowed to evaporate and alcohol sponges are therefore used in fevers. It is also a *rubefacient* and is included in liniments. Alcohol (50 per cent) is employed in bed-ridden patients in order to prevent *decubitus ulcers.* It is also used to *decrease sweating* and is an ingredient of many anhidrotic and astringent lotions. As an *antiseptic,* alcohol (70 per cent) is employed chiefly on the skin but also for instruments. In *phenol skin burns,* alcohol should be used immediately as a wash if castor oil is not available as a solvent. It is not to be employed as a lavage when phenol has been swallowed (page 829).

Injection for Relief of Pain. Strong alcohol may be injected around nerves or ganglia for the relief of pain. In the treatment of *angina pectoris,* injection of alcohol (two cc of 95 per cent) into stellate and upper dorsal sympathetic ganglia is often preferable to and certainly much safer than ganglionectomy. In *trigeminal neuralgia,* injection of alcohol into the affected nerve at its exit from the skull will often relieve pain for many months. In the pain produced by inoperable *carcinoma, tuberculous laryngitis,* etc., alcohol injection of the regional nerves is a valuable procedure. The agonizing itching of *pruritus ani* may be relieved by the subcutaneous or intracutaneous injection of alcohol in the afflicted area. Epidural injection of alcohol in the sacral region may be utilized to relieve the intractable pain of *pelvic carcinoma* before chordotomy is resorted to (Saltzstein, 1938).

Alimentary Tract. Alcoholic beverages, if enjoyed by the patient, may be given before meals as a *carminative* to improve appetite and digestion. This practice is especially useful in convalescent and debilitated or elderly people. In flatulence and colic, alcohol may give relief. The reflex stimulation arising from alcohol in the mouth, throat and stomach is utilized to treat *fainting.*

Systemic Uses. Alcohol acts as a *hypnotic* and *antipyretic* and is widely employed for these purposes by the laity. Alcoholic beverages, such as milk punches and eggnogs, are sometimes valuable for convalescents as rapidly assimilable sources of *energy.* Whisky or champagne may be the only food tolerated by febrile, restless patients. A hot toddy before bedtime is an old-fashioned remedy for *insomnia.* It may often produce results where other agents fail, due perhaps to the feeling of well-being which mild cortical depression and freedom from worry produce. Alcohol is used to cause vasodilatation in persons with *peripheral vascular* *disease* and its administration in *coronary artery disease* to lessen the frequency and severity of anginal attacks is quite valid. Alcohol is one of the few effective coronary vasodilators and is considered the best drug for angina pectoris. "Whisky and soda" is perhaps the alcoholic drink of choice for cardiac patients. Beer and cold drinks should be avoided.

The use of alcohol to check a *"cold"* deserves special mention. For generations, alcoholic beverages have been used to abort the development of impending "head colds," especially after chilling by exposure to inclement weather. Without contending that such a practice is effective or that it can stay the self-limited course of the common cold, it should be stated that alcohol has certain actions which, though not indispensable, may be of benefit. The vasodilatation resulting from alcohol aids in reestablishing the circulation in chilled cutaneous and mucosal surfaces. Also, if alcohol makes the patient drowsy or sleepy so that he stays in bed whereas otherwise he would be ambulatory, it may serve a useful purpose. Hamburger (1936) has for years humorously advised the following therapy, culled from an old English book, to be instituted at the first inkling of a cold, namely, to hang one's hat on the bedpost, drink from a bottle of good whisky until two hats appear, and then get into bed and stay there.

Contraindications. In hepatic and renal disease, alcohol should probably not be used. Ulceration of the gastro-intestinal tract or hyperacidity giving rise to digestive complaints is also a contraindication. Alcohol should not be taken by epileptics. In acute infections of the urinary tract, alcoholic beverages are to be avoided. Alcohol should be forbidden to patients who may easily become addicted to it. The use of alcohol in the presence of any particular disease is a matter which the physician must decide in each individual case.

Acute Alcoholic Intoxication

The characteristic signs and symptoms of acute alcoholic intoxication are well known. Nevertheless the mistaken diagnosis of drunkenness is often made in patients who appear inebriated but have not ingested alcohol. Great care should be taken to make certain that the patient's symptoms are due to alcohol. For example, approximately 10 per cent of 1159 consecutive cases with the preadmission diagnosis of acute alcoholism were found not to have ingested alcohol. Barbital, paraldehyde, cardiovascular accidents, schizophrenia and fractured skull, in the order named, were the most common causes for the erroneous diagnosis (Jetter, 1938). The odor of the breath is a notoriously unreliable guide and may often be seriously misleading. For medicolegal purposes, the concentration of alcohol in the blood, urine, saliva or exhaled air should be determined.

In severe intoxication, alcohol manifests an anesthetic action. The patient is stuporous or comatose. The skin is cold and clammy, the body temperature low, the respirations slow and noisy, the pupils normal or dilated, and the heart rate accelerated. If this condition persists for eight or ten hours, hypostatic pneumonia or increased intracranial pressure may intervene. Death is rare unless unconsciousness continues for many hours or trauma or infection complicates the case. Recovery is jeopardized if deep coma persists for over 12 hours.

Treatment. The patient should be kept warm. The stomach may be lavaged through a tube, but care must be taken to prevent aspiration of the return flow. Apomorphine should not be employed as an emetic because in itself it is depressant, after brief stimulation, and thus adds to the depression due to the alcohol. Caffeine is an effective antagonist to alcohol. It can be given rectally as strong black coffee, or caffeine with sodium benzoate (0.5 gram) may be injected intramuscularly. Ephedrine and other stimulants may also be employed. The value of metrazol has been emphasized by the report of Orenstein and coworkers (1939). If the respiration is greatly depressed, inhalation of carbon dioxide and oxygen may be necessary. Increased intracranial pressure due to cerebral edema is treated by the usual medical measures outlined under methyl alcohol poisoning. The promising results obtained with combined glucose and insulin therapy by Goldfarb, Bowman and Parker (1939) in acute alcoholic intoxication have already been presented in detail. In other respects, treatment does not differ greatly from that of toxic depression caused by anesthetics or hypnotics, and reference should be made to the therapy of barbiturate and morphine poisoning. The posture of the patient should be changed frequently in order to prevent hypostatic pulmonary complications. Postalcoholic headache and gastritis also require attention.

Chronic Alcoholism

The effects of the chronic use of immoderate amounts of alcohol on the organs of the body, length of life, fertility, and character of the progeny have already been discussed. The signs and symptoms of chronic alcoholism vary and may include those of gastro-enteritis (anorexia, nausea, vomiting and diarrhea); dilatation of skin capillaries, especially those of the face; loss of weight, malnutrition and cachexia; alteration in personality, delirium tremens, mental and moral deterioration; alcoholic cirrhosis, pellagra, polyneuritis, optic atrophy, and coincident serious organic disorders due to lowered vitality and resistance.

Treatment. Alcoholic patients as a rule are either hereditary defectives (often mentally deficient) or psychopathic personalities. Taking away the whisky bottle does not cure a drunkard. Wide personality and environmental readjustments are usually necessary. The major points to be followed in treatment are as follows: (1) Hospitalization in special nursing homes or retreats is often essential. (2) Adequate medical supervision and nursing care are paramount and should be undertaken only by those trained for this work. (3) Gradual withdrawal of alcohol is the safest procedure and lessens the danger of delirium tremens. (4) Proper sedation is an important part of symptomatic therapy. Paraldehyde and chloral hydrate are particularly helpful. Belladonna alkaloids are often used, as in the treatment of morphine addiction. (5) Psychotherapy, maintenance of nutrition and general hygiene, and firm but sympathetic management are essential.

Relapses are frequent in addicts to alcohol, although the prospects of cure are more promising than with morphine or cocaine addicts. A special problem arises in chronic drinkers who develop an *acute alcoholic psychosis*. This may last for days or even months and is characterized by auditory hallucinations, delusions of persecution, and suicidal or homicidal tendencies. The patient with an acute alcoholic psychosis should be institutionalized and treated as an acutely insane person.

DELIRIUM TREMENS

Delirium tremens is a syndrome seen in chronic alcoholism and confined to heavy drinkers. It may occur without apparent cause but usually starts after a particularly heavy bout of drinking, after trauma or fracture, during the course of an acute infection, or upon attempts to withdraw the alcohol. It represents an acute psychotic episode.

Symptoms. Prodromes of restlessness and insomnia may precede the onset of delirium tremens by several days. The two characteristic symptoms are tremors of the entire body and an acute delirium. From these features, the disorder derives its name. The delirium consists chiefly of visual and not auditory hallucinations, as in acute alcoholic insanity. These hallucinations are very real and terrifying. In fact, they are so realistic, that after recovery it is difficult to convince the individual that his experiences were illusory. The sufferer is entirely disoriented as to time and place but not as to person.

Other symptoms and signs are referable to the marked exhaustion which results from the constant movement, and the dehydration and malnutrition from the lack of water and food. The stage of excitement may continue for several days, and the patient may not eat, drink or sleep. Also, cerebral edema is not uncommon, and choked discs, headache, vomiting and coma may follow. Death can easily occur from exhaustion or intercurrent infection, and usually results from heart failure or hypostatic pneumonia. The mortality rate is high. If recovery occurs, it is gradual and delirium may be followed by a period of stupor.

Treatment. Successful treatment consists in giving encouragement and reassurance, and competent and sympathetic nursing care. It is imperative to quiet the patient and, if at all possible, to put him to sleep. If sleep lasts for seven or eight hours, the outlook is hopeful. Paraldehyde, given orally or rectally in doses of from 10 to 15 cc two or three times daily, is one of the best hypnotic agents in delirium tremens. Chloral hydrate in doses of two or three grams may also be used. Morphine should not be given because it increases intracranial pressure. If the patient is extremely restless and the usual measures to produce sleep have failed, one of the shorter-acting barbiturates may be given intravenously in the smallest amount necessary to give the desired result. Sodium amytal or pentobarbital may be used and is especially indicated if the patient is unmanageable. Given early, this may prove to be the best therapy. Once the patient is asleep, he should not be disturbed for any reason.

The patient should be kept in bed and warm. Special provision is made to insure an adequate food intake. The diet should be liquid or soft, and high in carbohydrate, calories and vitamins. If acidosis is present, this must be combated by the usual measures. Alcohol should be abruptly and completely withdrawn, despite the older practice of giving not only alcohol but also making certain that it was the same kind of beverage to which the patient was accustomed.

If there is evidence of increased intracranial pressure due to cerebral edema, a hypertonic solution of dextrose should be injected intravenously. Spinal fluid drainage, however, is probably to be preferred and some employ this measure routinely in all cases of delirium tremens (*see* Cline and Coleman, 1936). As much fluid is drained off as is readily removable, but the drainage should be done slowly. Other workers, however, believe that patients with delirium tremens should routinely receive from 3000 to 4000 cc of fluid daily unless fluids are specifically contraindicated. Thus Bowman, Wortis and Keiser (1937), from an extensive experience, advise that attention be given to supplying ample fluid and electrolyte and that lumbar puncture be done for diagnosis only and not for therapy. A similar opinion is advanced by Thomas, Semrad and Schwab (1939) who, in a carefully controlled study of the effects of dehydrating measures in delirium tremens, found that somewhat better results were obtained by giving ample fluids than by spinal drainage and fluid restriction, but that the difference was not striking. Likewise, Piker (1939) concluded that fluids should be neither restricted nor forced. His study consisted of 300 consecutive cases of delirium tremens divided into two equal groups, half of the patients receiving less than 1000 cc of fluids daily and the remainder receiving from 3000 to 4000 cc daily, treatment otherwise being similar. The number of deaths and the average duration of the illness were the same for the two groups. Many patients with delirium tremens are dehydrated when first observed and, by actual measurement, do not have increased intracranial pressure. To restrict fluids in these individuals may do harm. Nearly all observers, regardless of their views on the question of fluids, lay greatest emphasis on the importance of food and sleep.

Supportive treatment is supplied as needed. The practice of routine digitalization has no rational basis in the therapy of delirium tremens. Subdigitalization may be carried out when patients appear to be bad cardiac risks, and digitalization completed if congestive heart failure appears. It has been suggested that the intravenous administration of thiamine facilitates recovery from delirium tremens (Kiene and coworkers, 1940) but this point requires substantiation. There is also an encephalopathic syndrome which occurs in chronic alcoholic addicts which may be due to a deficiency of nicotinic acid (page 1258).

METHYL ALCOHOL

Methyl alcohol (CH_3OH) is known also as *wood alcohol* and *Columbian spirit.* It is the simplest of the alcohols.

Uses. Methyl alcohol is widely employed industrially as a solvent and occasionally as an adulterant in ethyl alcohol. It has no medicinal uses and is purely of toxicological interest. Poisoning can occur from its ingestion or from industrial exposure. During prohibition years in the United States, serious or fatal poisoning from methyl alcohol was not uncommon.

Fate in the Body. Methyl alcohol is longer-acting and more slowly oxidized in the body than ethyl alcohol. One-third of it still remains in the tissues forty-eight hours after ingestion. Within this two day period, approximately 40 per cent of the methyl alcohol is oxidized, 20 per cent is excreted unaltered through the lungs and three per cent is excreted as such in the urine. It is oxidized to formic acid ($HCOOH$) which is also excreted in the urine.

Methyl Alcohol Poisoning. Poisoning due to methyl alcohol results from a combination of the following factors: (1) central nervous system depression similar to that produced by ethyl alcohol; (2) acidosis due to the production of formic acid; (3) cerebral edema; (4) a specific toxicity of methyl alcohol for the optic nerve.

Symptoms. Inebriation is a prominent symptom of methyl alcohol intoxication. Violent gastric pains and vomiting are quite common and are due to the irritant action of methyl alcohol. Vision is disturbed quite early and the pupils are dilated and usually do not react to light. Dyspnea and cyanosis are prominent and acidosis must often be combated. Direct cardiac depression occurs and is due to both methyl alcohol and formic acid. Marked and protracted delirium is not unusual. Respiratory and circulatory failure, collapse and coma then ensue. Death may be delayed for several days following the onset of coma. If death does not occur, recovery is quite slow. This prolonged period of intoxication is in sharp contrast to that produced by ethyl alcohol. If the patient recovers, he may be totally blind. Once damaged, the vision usually shows no great improvement. Methyl alcohol is apparently toxic to both the optic nerve and retinal cells. Susceptibility to optic damage varies greatly. It may result from as little as 15 cc of methyl alcohol.

Treatment. The stomach should be washed and a four per cent solution of sodium bicarbonate may be left in the stomach to aid in the treatment of acidosis and to lessen gastric irritation. If abdominal pain is severe, morphine should be used. For delirium, scopolamine hydrobromide, in 0.2 to 0.5 mgm dosage, may be given. The patient should be kept warm and nutrition maintained. Acidosis and shock should be treated in the manner outlined elsewhere. Cerebral edema, when present, is combated by hypertonic intravenous glucose or sucrose (50 to 100 cc of 50 per cent solution, repeated as needed), lumbar puncture with removal of 50 to 75 cc of spinal fluid, magnesium sulfate orally in 30 to 60 gram doses, and restriction of fluid intake. The remainder of the treatment is supportive and symptomatic. Caffeine, ephedrine, coramine, and artificial respiration may be necessary if respiratory failure occurs.

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CHAPTER 9

HYPNOTICS AND SEDATIVES

I. THE BARBITURATES

The barbiturates comprise an important and valuable group of central nervous system depressants frequently prescribed by physicians and widely used by the laity. New barbiturates are constantly being introduced, usually under confusing trade names, and claims are often made that a particular compound is superior regarding potency, margin of safety or duration of action. At times it appears that the only goal in producing new barbiturates has been to obtain their exclusive sale by the manufacturer.

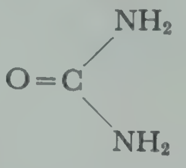
The proper selection and rational use of the barbiturates rest upon an intimate knowledge of their pharmacology and toxicology, as well as an acquaintance with the important variations in action and toxicity manifested by certain individual members. In this section, therefore, the barbiturates will be discussed as a group and important differences in the behavior of specific barbiturates will be mentioned as occasion arises. This is possible for the reason that many members of the group do not differ significantly from barbital or phenobarbital in their pharmacology or therapeutic uses. Indeed, the major variations occur in the duration of depressant action and in the suitability for use as an intravenous anesthetic.

The pertinent literature on the subject of the barbiturates has been reviewed by Lundy and Osterberg (1929) and by Tatum (1939).

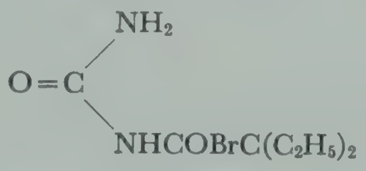
History. Barbital, the oldest barbiturate, was first introduced into medicine by Fischer and von Mering under the trade name of *veronal* in 1903. Barbital has survived many years of clinical trial, has long been official in the U.S.P., and is still one of the best hypnotics. The second oldest barbiturate is phenobarbital, introduced into therapeutics several years after barbital under the trade name of *luminal*. It too has proved its worth, and for many purposes deserves preference over certain newer barbiturates, the ultimate clinical value of which remains to be established. In the following years more than a score of barbiturates were synthesized and marketed for clinical use. The chief advantage of several of these drugs is their shorter duration of action as compared with barbital and phenobarbital. The latest advance has been the substitution in the barbituric acid molecule of sulfur for the oxygen on the urea carbon, and this has given rise to an entire homologous series of compounds with distinctive properties and special uses.

Chemistry. Barbituric acid is malonylurea, a combination of malonic acid and urea. Urea is not in itself a central depressant. Substitution products of urea, however, may have definite hypnotic power. This is true of the *ureides* which are formed from the combination of urea and organic acids.

Ureides fall into two groups, the *monoureides* and *diureides*. The monoureides are compounds in which only one of the amino groups of urea is condensed with a carboxyl group. An example of a sedative monoureide is *carbromal* (U.S.P.). Its formula and relation to urea are as follows:



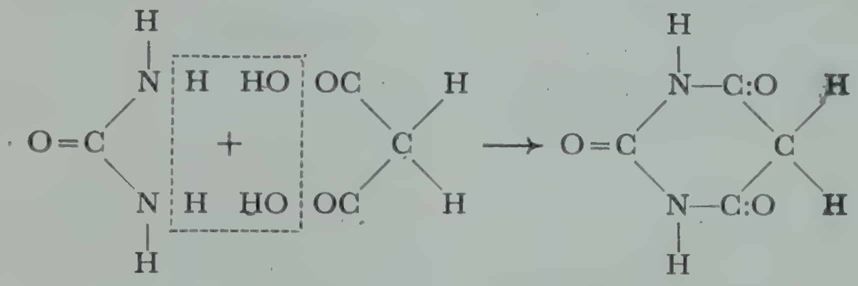
Urea



Carbromal

The monoureides are decomposed in the body to urea and are readily eliminated, their margin of safety thus being large. The clinical use of monoureides has given disappointing results due to the feeble depressant effects.

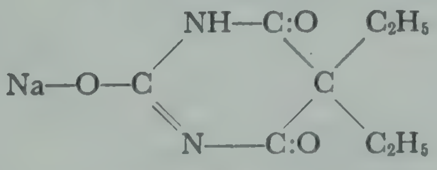
The diureides, which result from the combination of organic acid radicles with both amino groups of urea, are more powerful hypnotics. The main diureide from a pharmacological point of view is *barbituric acid,* the condensation product of urea and the dicarboxylic malonic acid, as shown in the following reaction:



Urea + Malonic acid Barbituric acid (Malonylurea)

The two hydrogens of barbituric acid which are indicated in bold-faced type in the foregoing formula are quite reactive and can be replaced by various radicles. Many series of chemical derivatives of barbituric acid have been prepared and are called *barbiturates* or *barbituric acid derivatives.* Barbital itself results from the replacement of the two **H's** by ethyl groups to form diethylbarbituric acid (diethylmalonylurea). If an ethyl group of barbital is replaced by a phenyl group, phenobarbital is obtained. Most of the barbiturates employed clinically have alkyl groups substituted in the barbituric acid nucleus; but other radicles can easily be inserted and two compounds (evipal and phanodorn) have a complex cyclic radicle replacing a reactive hydrogen (Table 5).

Despite the fact that barbituric acid derivatives do not contain a carboxyl group they have acidic properties due to the fact that the lactam form (—CO—NH—) is in equilibrium with the lactim form (—C(OH):N—), the hydrogen of which is readily dissociated, allowing formation of salts with alkalis. For example, the sodium salt of diethylbarbituric acid (sodium barbital) may be considered to have the following structural formula:



Sodium Barbital

Table 5
BARBITURATES AVAILABLE FOR CLINICAL USE

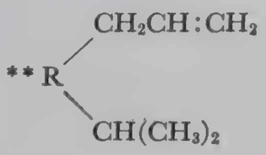
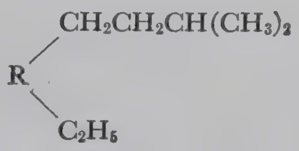
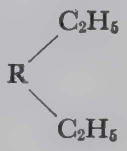
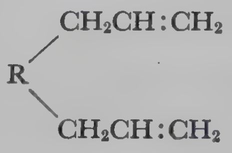
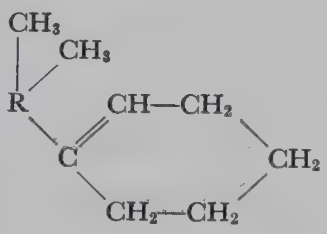
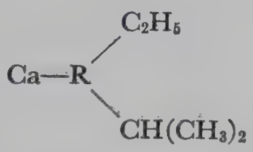
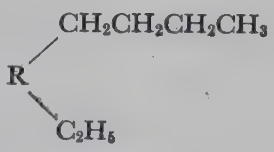
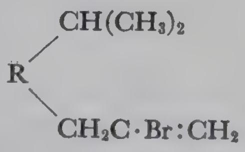
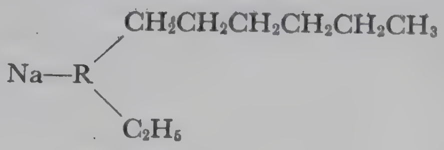
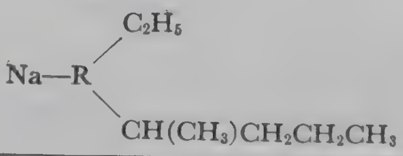
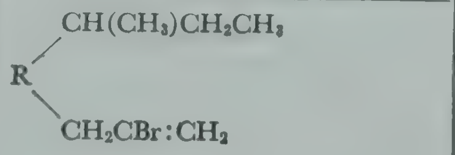
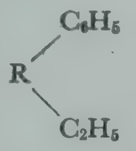
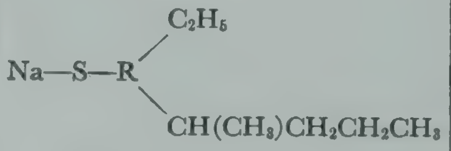
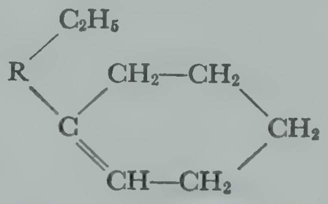
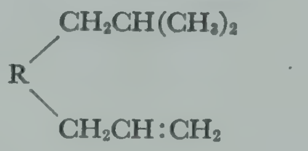
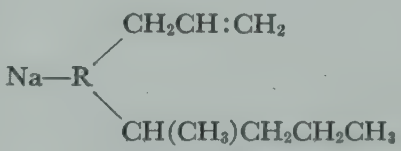
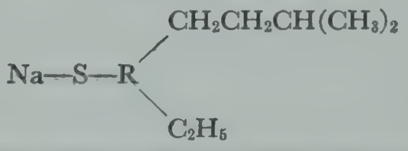
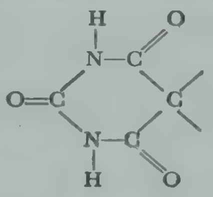
Barbiturate	Status	Chemical Name	Structural Formula	Average Adult Hypnotic Dose
				Grams
Alurate *	N.N.R.	Allylisopropylbarbituric acid	 $** R\begin{array}{l}\diagup CH_2CH{:}CH_2\\ \diagdown CH(CH_3)_2\end{array}$	0.065–0.13
Amytal *	N.N.R.	Isoamylethylbarbituric acid	 $R\begin{array}{l}\diagup CH_2CH_2CH(CH_3)_2\\ \diagdown C_2H_5\end{array}$	0.1–0.3
Barbital *	U.S.P. B.P.	Diethylbarbituric acid	 $R\begin{array}{l}\diagup C_2H_5\\ \diagdown C_2H_5\end{array}$	0.3–0.5
Dial	......	Diallylbarbituric acid	 $R\begin{array}{l}\diagup CH_2CH{:}CH_2\\ \diagdown CH_2CH{:}CH_2\end{array}$	0.1–0.3
Evipal *	......	N-methylcyclohexenylmethyl barbituric acid		0.25–0.4
Ipral Calcium *	N.N.R.	Calcium ethylisopropylbarbiturate	 $Ca{-}R\begin{array}{l}\diagup C_2H_5\\ \diagdown CH(CH_3)_2\end{array}$	0.12–0.25
Neonal	N.N.R.	n-Butylethylbarbituric acid	 $R\begin{array}{l}\diagup CH_2CH_2CH_2CH_3\\ \diagdown C_2H_5\end{array}$	0.05–0.1
Nostal	N.N.R.	Isopropyl bromallyl barbituric acid	 $R\begin{array}{l}\diagup CH(CH_3)_2\\ \diagdown CH_2C\cdot Br{:}CH_2\end{array}$	0.1–0.3
Ortal Sodium	N.N.R.	Sodium n-hexylethyl barbiturate	 $Na{-}R\begin{array}{l}\diagup CH_2CH_2CH_2CH_2CH_2CH_3\\ \diagdown C_2H_5\end{array}$	0.2–0.4
Pentobarbital Sodium	U.S.P.	Sodium ethyl (1-methylbutyl) barbiturate	 $Na{-}R\begin{array}{l}\diagup C_2H_5\\ \diagdown CH(CH_3)CH_2CH_2CH_3\end{array}$	0.1–0.2

Table 5 (*Continued*)

Barbiturate	Status	Chemical Name	Structural Formula	Average Adult Hypnotic Dose
Pernoston	N.N.R.	1-methylpropyl-β-bromallyl barbituric acid	 $CH(CH_3)CH_2CH_3$ R $CH_2CBr:CH_2$	0.2
Phenobarbital *	U.S.P. B.P.	Phenylethyl-barbituric acid		0.1–0.2
Pentothal Sodium	N.N.R.	Sodium ethyl (1-methylbutyl) thiobarbiturate	 C_2H_5 Na—S—R $CH(CH_3)CH_2CH_2CH_3$	....
Phanodorn	N.N.R.	Cyclohexenylethyl barbituric acid	 C_2H_5 R CH_2—CH_2 C CH_2 CH—CH_2	0.1–0.2
Sandoptal	N.N.R.	Isobutylallyl barbituric acid	 $CH_2CH(CH_3)_2$ R $CH_2CH:CH_2$	0.2–0.4
Seconal	......	Sodium allyl (1-methylbutyl) barbiturate	 $CH_2CH:CH_2$ Na—R $CH(CH_3)CH_2CH_2CH_3$	0.1–0.2
Thio-ethamyl †	......	Sodium isoamyl ethyl thio-barbiturate	 $CH_2CH_2CH(CH_3)_2$ Na—S—R C_2H_5	....

* Sodium salt also available

** R represents the bivalent barbituric acid radicle:



H
O
N—C
O═C
C
N—C
H
O

† Supplied commercially in Great Britain.

An entirely new series of barbiturates has been obtained by the substitution of sulfur for the oxygen on the urea carbon. The compounds which result from the condensation of thiourea and malonic acid are known as *thiobarbiturates*, the unique properties of which are described later.

In Table 5 are presented the chemical names and formulas of the official and N.N.R. compounds available in the United States, as well as the more commonly employed preparations not as yet accepted by the Council on Pharmacy and Chemistry. It will be observed that only barbital, phenobarbital and pentobarbital are official U.S.P. drugs. The proprietary barbiturate known as *nembutal* is chemically identical with U.S.P. pentobarbital sodium (*see* Report of the Council, 1937). The only N.N.R. (1940) thiobarbiturate is *pentothal,* the sulfur homologue of U.S.P. sodium pentobarbital. *Dial,* diallylbarbituric acid, is no longer included in the N.N.R. The ending "al" is common, with a few exceptions, to all of the barbiturates.

Relation Between Chemical Structure and Pharmacological Action. Several hundred barbiturates have been prepared but less than one hundred have been carefully studied for their pharmacological properties. From these studies certain general principles of chemical structure as related to pharmacological action are fairly well established, some of which may be briefly presented. Both of the reactive H's of barbituric acid must be replaced by alkyl or aryl groups in order to obtain compounds with hypnotic properties. An increase in the length of one or both alkyl side-chains results in enhanced potency and diminished duration of depression; but if the side-chains substituted for the reactive hydrogens of barbituric acid are too long (*i.e.,* over five or six carbon atoms), the hypnotic potency decreases and convulsive properties may appear. Alkyl groups attached to both of the *N* atoms also tend to yield convulsant compounds. In general, barbiturates with alkyl radicals are relatively stable in the body, while those with complex cyclic radicals, such as evipal, are unstable and readily destroyed. Derivatives of thiobarbituric acid are likewise rapidly decomposed in the body and therefore are short in duration of action. Compounds with branched side-chains are likely to manifest a brief duration of depressant effects and unsaturation in the side-chain tends to result in increased hypnotic activity. Isomers may exhibit quite different pharmacologic properties. For example, an anesthetic dose of amytal inhibits the cardiac action of the vagus whereas an equivalent amount of its isomer, pentobarbital, apparently lacks this effect. The substitution of a phenyl for an ethyl radical in barbital is the basis for the specific anticonvulsant property of phenobarbital in epilepsy. The fate of barbiturates in the body depends on their chemical structure. For example, barbital and phenobarbital are excreted in the urine, whereas amytal, pentobarbital, evipal and thiobarbiturates are largely destroyed in the body. It is thus evident that slight changes in chemical structure of the substituted groups in the barbituric acid nucleus or the replacement of the urea oxygen by sulfur affect significantly the action, fate and excretion of the resulting compounds.

Pharmacological Actions

The major action of the barbiturates and the one for which they are employed in medicine is central nervous system depression, essentially similar in character to that caused by the hydrocarbon anesthetics of the methane series.

Central Nervous System. All the numerous barbiturates have the same general type of depressant action on the cerebrospinal axis. They may be considered, at least from a clinical point of view, as differing mainly in the dose in which they are effective, in speed of onset of action, in duration of the hypnotic effects and in their usefulness for specific purposes. Any degree of depression from slight sedation to deep coma can be obtained with the barbiturates. The central depressant effects are therefore employed to produce calmness, to induce sleep, to depress the motor cortex and thus inhibit convulsions, and to cause partial or complete surgical anesthesia. The intensity of action obtained depends not only upon the particular barbiturate selected and the dose and route of administration employed, but also in large measure upon the reflex excitability of the patient's nervous system (page 49).

Hypnosis. The barbiturates are used more for the production of sleep than for any other purpose. With adequate oral doses of nearly any barbiturate, sleep occurs in from 20 to 60 minutes. The sleep is dreamless and, as a rule, refreshing. When the longer-acting barbiturates are employed there may be a "hangover" upon awakening.

Analgesia. The barbiturates differ sharply from both the opium alkaloids and analgesics, such as the salicylates, in that they lack the property of obtunding pain sense without loss of consciousness. The barbiturates are thus not analgesics and cannot be depended upon to produce sedation or sleep in the presence of pain. Indeed, if given alone under this circumstance, they are likely to induce delirium. Nevertheless, when they are combined with analgesic drugs such as the salicylates, they render the analgesia more effective. The reverse is not true, however, and in the absence of pain the analgesic drugs do not potentiate the hypnotic action of the barbiturates.

Anticonvulsant Action. In anesthetic doses, all of the barbiturates are capable of inhibiting convulsions, such as in strychnine poisoning, tetanus and status epilepticus. Phenobarbital, however, has a selective action on the *motor cortex* in epileptic patients when given in sedative doses, but this property is not shared by other members of the group. The specific corticomotor depression produced by phenobarbital has been experimentally demonstrated by several workers. Keller and Fulton (1931) found that this drug alone, of several barbiturates studied, completely abolished the electrical excitability of the motor cortex of monkeys when doses sufficient to cause full surgical anesthesia were employed. This was not true of anesthesia with dial, amytal, barbital, chloral hydrate or avertin. Merritt and Putnam (1938) noted that phenobarbital in sedative doses was much more effective than bromide in preventing convulsions in cats, electrically induced by stimulation of the motor cortex, and that other barbiturates did not increase the corticomotor threshold. This problem is further discussed under the use of phenobarbital in epilepsy.

Anesthesia. In sufficient doses, barbiturates can produce surgical anesthesia characterized by the same type of irregularly descending depression described for the volatile anesthetics. The actions of barbiturates on the brain and spinal cord, however, differ in many respects from those of the volatile agents. Some of these differences have been elucidated by experimental studies of the electrical responses (action potentials) of the brain under barbiturate anesthesia. For example, Derbyshire, Rempel, Forbes and Lambert (1936) found that marked electrical responses to sciatic nerve stimulation occurred in the cortex of cats under deep pentobarbital and dial (or avertin) anesthesia, but that these responses did not appear in deep ether anesthesia. It was concluded that afferent pathways leading to the cortex were blocked by deep ether anesthesia, but that barbiturate anesthesia, while inhibiting the spontaneous activity of the cortex, left it accessible to afferent stimuli. Forbes and Morison (1939), in a continuation of these experiments, have attempted more closely to localize the cerebral pathways involved. Their results, however, are somewhat at variance with those obtained by Bremer (1936, 1937), who believes that the barbiturates act selectively on internuncial cortical neurones rather than on afferent or motor paths, resulting in a functional "deafferentation" of the cerebral cortex. The cortical oscillograms obtained by Bremer after administration of a barbiturate resemble those reported for man in natural sleep.

Stages of Anesthesia After Intravenous Administration of Barbiturates. When the barbiturates are given intravenously for the production of anesthesia, the stages described in detail for the inhalation anesthetics are not readily delineated and indeed the induction phase may be impossible to detect. The patient appears to "fall asleep" quite suddenly during the course of a fairly rapid injection, sleep often interrupting the patient's conversation in the middle of a sentence. Only when the injection of a barbiturate is performed slowly can the stages of anesthesia be discerned. The induction period then resembles, in a general way, that noted with the inhalation anesthetics. The stage of surgical anesthesia is characterized by diminution or disappearance of superficial and deep reflexes, constricted pupils and fixed eyeballs, relaxation of the pharyngeal structures with falling backward of the tongue, shallow respiration and a fall in blood pressure, especially marked in patients with vascular hypertension. The signs vary with the amount of barbiturate administered and with the individual patient. When an overdose of drug is given, muscular flaccidity is marked, respirations are seriously depressed and the blood pressure falls early and rapidly to shock levels. *Recovery* is sometimes characterized by an initial period of restlessness, during which the patient may be irrational and hyperactive. Others experience a long period of sleep and immobility lasting for many hours and enhancing the danger of hypostatic pneumonia.

Locus of the Central Depressant Actions of Barbiturates. Despite the large amount of investigative work designed to elucidate the chief site of action of barbiturates on the cerebrospinal axis, many questions remain unanswered. It has been the custom of some pharmacologists to divide soporific drugs into two large groups, those acting mainly on the cortex and those affecting chiefly the diencephalic vegetative centers regulating sleep. The so-called cortical hypnotics were believed to be alcohol, paraldehyde, amylene hydrate, chloralose, bromide and certain of the substituted urea derivatives. Alleged diencephalic somnifacients were chloretone, urethane and a variety of barbiturates.

The *clinical evidence* for the belief that barbiturates have a selective site of action rests on the observations that sleep induced by barbiturates closely resembles physiological sleep, that patients with chronic encephalitis lethargica may be quite resistant to these drugs and that phenobarbital may markedly aggravate the rigidity in patients with parkinsonism.

Evidence from *chemical analyses* for barbiturate in the brain has been advanced to support the claim that these agents have a subcortical locus of action on vegetative and sleep centers. Keeser and Keeser (1927, *et seq.*), using both chemical and histological methods, reported a localized deposition of barbiturates in the thalamus and corpus striatum, none being noted in the cortex, pons, cerebellum or medulla. Other investigators, however, have not substantiated these findings. For example, Koppanyi and his associates (1934) failed to obtain chemical evidence for a selective distribution of barbiturates. Indeed, their data suggest that these drugs are found in approximately equal concentration throughout the brain. It is perhaps pertinent to recall that the bromides are distributed uniformly throughout the extracellular fluids of the body, and that selective depressant actions can therefore depend on special sensitivity of certain nerve cells to chemical substances rather than on concentration gradients at different sites.

However, it cannot be denied that the barbiturates may selectively depress certain functions mediated by subcortical centers. Leiter and Grinker (1934), for example, studying vasomotor and respiratory reactions to electrical stimulation of the hypothalamus in cats, found that the responses were more readily elicitable under ether than under dial anesthesia. Again, Masserman (1937) observed that amytal anesthesia markedly diminished or completely abolished the motor, sympathetic and emotional mimetic responses in cats incident to the faradic stimulation of the hypothalamus. The local intrahypothalamic injection of amytal, in contrast, caused neither sleep nor any apparent change in the sympathetic and emotional responses. These facts would indicate that amytal affects hypothalamic functions by other than a local action. Also, it is well known that the barbiturates antagonize the analeptic effects of picrotoxin, ephedrine and benzedrine, drugs known to act on the brain stem. Furthermore, by the use of thermocouple measurements of temperature changes in cortical and subcortical loci, Pick and coworkers (*see* Feitelberg, Pick and Warsberg, 1939) have demonstrated that barbiturates selectively depress the brain stem before the cortex.

Attention has also been centered on the finer mechanism of action of barbiturates on the *spinal cord.* Porter and Allamon (1936), for example, found that barbital, phenobarbital, amytal and evipal raise the threshold to sensory stimulation in the spinal cat to many times the original value, depending on the dose used, and that this action is antagonized by strychnine. The barbiturate-strychnine antagonism and its clinical applicability are more fully discussed on page 261. The similarity between the effect of low spinal transection and barbiturate anesthesia has been demonstrated by Beecher, McDonough and Forbes (1939). Both procedures greatly decrease after-discharge and curtail "long-circuiting" of sensory impulses in the cord, barbiturates differing from ether anesthesia in this respect.

Respiration. Soporific doses of the barbiturates are only slightly depressant to respiration. The decrease in respiratory exchange is mainly the result of sedation or sleep. Larger doses, however, are directly depressant to the medullary respiratory center and to a lesser degree to the sino-aortic chemoreceptors. Both the rate and depth of breathing are decreased and the rhythm may be irregular. In Figure

12 is shown the respiratory effect of a large somnifacient dose of sodium pentobarbital (0.28 gram) in a normal adult. Within three-quarters of an hour after the oral ingestion of the drug, the respiratory depth had decreased and the respiratory minute volume was lowered by 22 per cent.

Death from poisoning by barbiturates, as a rule, is due to respiratory failure. Marked depression of respiration is very apt to attend the intravenous injection of barbiturates for anesthesia and is one of the major dangers of this route of administration. In addition to direct depression of the respiratory center respiration may be embarrassed either by pulmonary edema or hypostatic pneumonia, the former usually appearing early in acute poisoning from over-medication with the short-acting drugs and the latter occurring late in the course of poisoning by the longer-acting barbiturates.

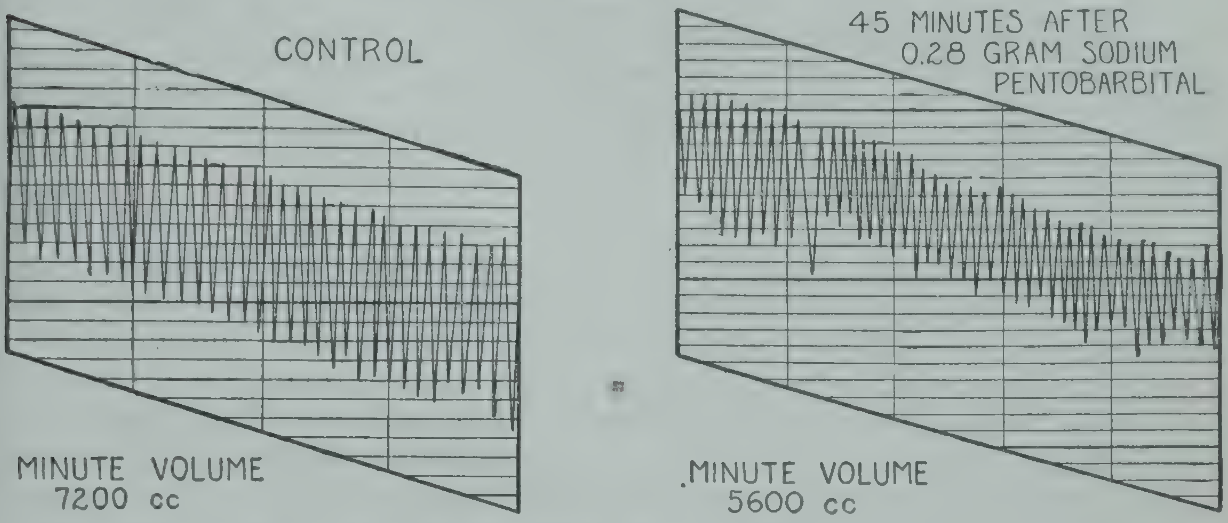


FIGURE 12. *The effect of a large hypnotic dose of sodium pentobarbital on the respiration.* Normal female, aged 62, 58 kg. Although the respiratory rate was not changed, the depth of respiration was significantly depressed, resulting in a 22 per cent decrease in respiratory minute volume. (Courtesy of Dr. Ralph M. Waters, Dept. of Anesthesia, University of Wisconsin.)

Cardiovascular System. Ordinary hypnotic doses of barbiturates have little effect on the cardiovascular system. The blood pressure and pulse rate may fall somewhat as a result of the quieting action or sleep produced by the medication. A sharp fall in blood pressure may result from the rapid intravenous injection of a relatively safe dose of a barbiturate, but the hypotension is transitory if the dose is not too large. Large doses of barbiturates depress the central vasomotor center and peripheral vasodilatation and hypotension follow. Barbiturates also can produce dilatation of the finer blood vessels by a direct effect on their musculature, and excessive concentrations may dilate and injure capillary beds to such an extent that shock ensues. The cerebral vessels tend to be dilated by the barbiturates, but the degree of vasodilatation varies with the individual members of the group. For example, Fulton and Keller (1932) observed that cerebral operations on chimpanzees were facilitated by the use of dial because of the vasoconstriction of cortical vessels produced, whereas amytal and pentobarbital were inclined to cause vasodilatation. Cardiovascular reflexes are diminished by anesthetic doses of the barbiturates and the carotid sinus mechanism is depressed.

The barbiturates, even when used intravenously for anesthesia, do not appear to be directly toxic to the myocardium, or seriously to alter cardiac rhythm or conduction.

In dogs and cats, the heart rate may be accelerated, the *T* wave transiently inverted, and a preexisting sinus arrhythmia decreased (Hafkesbring and MacCalmont, 1938). Experimentally in dogs, barbital appears to protect against ephedrine-induced arrhythmias (Meek and Seevers, 1934) and amytal against cardiac irregularities caused by cyclopropane anesthesia (Robbins and coworkers, 1939). Cardiac irregularities have been noted by Gruber and his associates (1938) to occur consistently in laboratory animals after the injection of thiobarbiturates. Betlach (1937), however, noted no significant electrocardiographic changes in dogs after pentothal, and Kohn and Lederer (1938) only occasionally observed cardiac irregularities from pentothal in a variety of animals. Also, Volpitto and Marangoni (1938), using pentothal and sodium thio-ethamyl as well as evipal, in 17 intravenous anesthesias in 12 patients, found no deviation from the normal in the electrocardiogram. Anesthesia with thiobarbiturate did not tend to sensitize the heart to epinephrine, although a tachycardia accompanies the anesthesia. The effects of thiobarbiturates on the cardiovascular system of man deserve considerably more study, although the available evidence indicates that the clinical use of these drugs causes no significant disturbances of cardiac rhythm.

Gastro-intestinal Tract. The barbiturates tend to decrease the general tonus of the intestinal musculature and the amplitude of rhythmic contractions as measured in experimental animals (Quigley and Phelps, 1934; Quigley, Barlow and Himmelsbach, 1934; Gruber and associates, 1936). Tournade and Joltrain (1936) found that, after evipal, stimulation of the vagus failed to produce the characteristic effects on the intestine. Whether the inhibition is due to a depression of the intrinsic ganglia or the enteric musculature is not known. Burstein (1939), however, has reported that after an initial phase of depression of intestinal movement following the intravenous injection of evipal, amytal, pentobarbital and thiobarbiturates in dogs with Thiry-Vella intestinal loops there occurred a more prolonged phase characterized by an increase both in tonus and contractions. The therapeutic effects of hypnotic doses of barbiturates in the relief of symptoms arising from the gastro-intestinal tract are attributable to central depressant actions.

Renal Effects. The barbiturates apparently have no direct effect on normal renal function. Urine formation, however, is influenced in at least two ways. Large doses of barbiturates have an antidiuretic effect and can inhibit water diuresis. Available evidence indicates that this action is probably a central one on the hypothalamic-pituitary system. It is not peculiar to barbiturates, however; it is also noted with other central depressants. The barbiturates can also affect urine secretion indirectly through the circulation. The hypotension which characterizes overmedication with barbiturate results in oliguria or anuria, and interrupts an important channel for excretion of these drugs.

Peripheral Autonomic Effects of Barbiturates. The barbiturates have a number of actions on organs innervated by the autonomic nervous system. These differ with the individual drug and with the species investigated. At present it cannot be stated with certainty what rôle, if any, the effect on autonomic structures plays in the clinical use of the barbiturates. Only a few of the accumulated experimental facts can be presented. A number of the barbiturates, given in anesthetic doses to animals, depress the electrical excitability of the vagus nerve to the heart, in some cases to the extent of complete block (Lieb and Mulinos, 1929; Garry, 1930; Koppanyi and coworkers, 1935). This parasympatholytic effect does not occur after the administration of thiobarbiturates, in which instance the cardiac responsiveness to vagal stimulation may even be enhanced (Linegar and associates, 1936; Gruber and coworkers, 1938). Although evidence suggests that the barbiturates have a curare-like action on vagal cardiac ganglia, they may also directly depress postganglionic fibers. Similarly, amytal has been reported to prevent the response of the submaxillary glands to stimulation of the chorda tympani (Stavraky, 1931), but here the action appears to be directly on the secretory cells whose response to acetylcholine as well as to nerve impulses is blocked by barbiturates.

Barbiturate anesthesia also interferes with the demonstration of the release of chemical mediators during nerve stimulation. For example, amytal and dial may interfere with the demonstration of the liberation of sympathin into the blood stream. Barbiturates have a markedly depressant or even paralyzing action on the proprioceptive mechanisms regulating vasomotor tone (Bouckaert and Heymans, 1937). Finally, the respiratory phenomena such as coughing, sneezing, hiccuping and obstructive spastic adduction of the vocal cords seen during clinical anesthesia with intravenously administered short-acting barbiturates may be due to hyperactive respiratory reflexes resulting from a central stimulatory effect on the vagus (Burstein and Rovenstine, 1938), and it has been suggested that atropine or scopolamine be administered prior to all such anesthesias.

Metabolic Rate and Body Temperature. The barbiturates tend to reduce somewhat the basal metabolic rate, although the effects of hypnotic doses in man have been insufficiently studied in this respect. Anderson, Chen and Leake (1930) reported that hypnotic doses of barbital, neonal, ipral and phanodorn, but not of amytal and phenobarbital, produced some decrease in oxygen consumption. Anesthetic doses of barbiturates, however, definitely lower oxygen consumption (Dameshek and coworkers, 1934; Shapiro, 1937). The usefulness of the barbiturates in patients with hyperthyroidism is based not on any specific effect on the elevated metabolic rate but rather on the sedative action.

Liver. Hepatic function is unimpaired by therapeutic doses of the barbiturates. Anesthetic doses of amytal, for example, cause no significant depression of hepatic function as measured in dogs and human beings by the bromsulfalein dye excretion test (Bourne and associates, 1930). In patients with liver damage, large doses of barbiturates may further injure the liver. The rôle of the liver in the detoxification of barbiturates is discussed under the fate of these drugs.

Miscellaneous Effects. The *uterus* is relatively resistant to the depressant effect of the barbiturates on smooth muscles, and hypnotic doses do not significantly impair uterine activity during labor. Full anesthetic doses, on the other hand, definitely decrease the force and frequency of uterine contractions (Gruber, 1937). More important in regard to the clinical use of barbiturates during labor is the depressant effect of the drug on the respiratory center of the infant, the placenta offering no barrier to the ready passasge of the chemical to the fetus.

The *cerebrospinal fluid pressure* is not influenced by hypnotic doses of barbiturates but may be decreased by larger amounts. Whereas Myerson and Loman (1932) found that amytal anesthesia in man caused no change in intracranial pressure, Horsley (1937) reports that of 100 patients anesthetized with the short-acting barbiturates, 99 manifested a fall of cerebrospinal fluid pressure to an average of about one-half of its previous value, this fall being succeeded by a slow rise.

The response of the *blood sugar* to medication with barbiturates varies considerably, dependent upon the particular drug selected, the dose and route of administration, the species being studied and the previous diet. In man, soporific doses do not significantly or consistently alter the level of blood sugar and these drugs are not contraindicated in patients with diabetes mellitus. The formed elements of the *blood* and the hematocrit are not significantly altered by hypnotic doses of barbiturates, but Searles (1939) has shown that amytal anesthesia in dogs causes a marked decrease in hemoglobin, erythrocyte count and cell volume, effects abolished completely by splenectomy and probably due to splenic dilatation.

Habituation and Tolerance. Addiction to the barbiturates, in the strict sense of the word, probably does not occur. Habituation, in contrast, is not infrequent and certain patients may experience craving and psychic disturbances after the barbiturate is withdrawn (*see* Lowy, 1934). This phenomenon, however, is rather characteristic of the hypnotic-sedative group of drugs. From an analysis of hospital data, Hambourger (1940) found that barbiturate "addiction" was fairly common, accounting for approximately one-tenth of all cases of drug addiction (excluding chronic alcoholism) received by hospitals in larger cities. However, only a third of the patients for whom information was recorded developed craving when the barbiturate was withheld, and none showed serious withdrawal symptoms. The control by state laws of the sale of barbiturates is an important factor in the prevention of their habitual use without medical supervision. At the present time, 27 states have laws regulating the sale of barbiturates (*see* the Bureau report, 1940).

Although a number of investigators have reported partial tolerance to occur in animals after the prolonged administration of barbiturates, a significant degree of tolerance to the barbiturates does not develop (*see* Stanton, 1936), and prolonged administration in human beings usually fails to diminish, or decreases only slightly, the hypnotic effects. Similarly, the toxic dose is not appreciably elevated after chronic medication. Clinical observations are borne out by some of the results of animal experimentation. For example, Swanson and coworkers (1937) noted no evidence of tolerance, withdrawal symptoms or decreased toxicity after a six-month period of administration of sodium amytal to dogs and monkeys.

Routes of Administration. *Oral.* The oral route of administration of barbiturates is the best from the standpoint of simplicity, safety and expense to the patient, and should be employed whenever possible. Other routes are resorted to only when special indications for their use exist. All the barbiturates (including thiobarbiturates) are satisfactorily absorbed from the intestinal tract, and only when the patient is moribund or uncooperative, or when the rapid onset of anesthetic effects of the drugs is desired, is parenteral administration used.

Rectal. The rectal administration of barbiturates is occasionally indicated, as in infants or in patients who are vomiting. The drug may be given in the form of a suppository or the soluble sodium salt may be incorporated in a retention enema. Thiobarbiturates are not given by the rectal route.

Subcutaneous and Intramuscular. When a rapid onset of action is required, as in patients with convulsions, the soluble sodium salts may be injected hypodermically. For this purpose, a 10 per cent sterile solution is employed. The solutions are not irritating when injected intramuscularly, provided the thiobarbiturates are not employed. The latter cannot be given subcutaneously or intramuscularly.

Intravenous. This route is by far the most dangerous and is reserved either for emergencies or for the production by competent anesthetists of surgical anesthesia of short duration. Once the drug has been injected, the degree of anesthesia can no longer be controlled by the physician, because elimination of the drug from the body is relatively slow. Therefore, the moment to moment control of anesthesia which characterizes the use of inhalation anesthetics and which accounts for their safety and preference, is lacking when the intravenous route is employed for barbiturates. When inhalation anesthesia is given, the amount of anesthetic to be used is readily ascertained from the response of the patient and the physical signs existing at any one moment. Withdrawal of the anesthetic results in a rapid lightening of the degree of depression. When barbiturates are injected intravenously, however, it is most difficult to judge in advance the amount to be given, and individuals vary considerably in their response. Reliance cannot be placed on fixed doses based on age and weight, and considerable experience is required to judge the amount to inject from the physical signs observed while the patient is entering surgical anesthesia. It must be remembered that in order to produce anesthesia, from 50 to 70 per cent of the fatal dose of barbiturate is administered.

The injudicious use of barbiturates by the intravenous route has resulted in a number of unnecessary accidents and deaths. An alarming fall in blood pressure to shock levels is sometimes observed, especially if the injection is performed too rapidly. Serious depression of the respiration is a constant danger of overdosage. The apparent ease of administration of an anesthetic by the intravenous route should not tempt one who is not thoroughly experienced in this field to employ barbiturates for intravenous anesthesia. The Council on Pharmacy and Chemistry in 1939 accepted for inclusion in N.N.R. barbiturates (pentothal) designed for use as intravenous anesthetics but properly warns that such use is potentially dangerous, should be undertaken only by experts for short operations and that facilities to combat respiratory and cardiovascular depression should be available. The value, dangers, contraindications, and technic of administration of pentothal sodium for intravenous anesthesia have been authoritatively reviewed by Ruth, Tovell, Milligan and Charleroy (1939).

As an example of the technic employed, that advised for pentothal sodium (N.N.R.) may be cited. Two to three cc of a five per cent solution (from 0.1 to 0.15 gram) are injected in approximately 10 to 15 seconds. The injection is then stopped in order to permit the complete effect to become apparent, which requires about 30 seconds. If relaxation has not occurred, an additional two or three cc may be injected at the same rate as before. If necessary, added increments of drug may be given at suitable intervals in order to maintain adequate anesthesia. The stages of anesthesia observed have been discussed.

Absorption, Fate and Excretion. *Absorption.* Absorption of the barbiturates occurs readily from the intestinal tract. The speed of absorption varies with the individual drugs; in general the rate is slower for the long-acting members and faster for the short-acting ones. Absorption also occurs readily from the rectum, subcutaneous tissues and muscles.

Fate. The distribution of the barbiturates in body tissues and fluids is poorly understood. After intravenous injection, the drug remains in the blood in detectable amounts for only a few minutes. Concentrations found in the brain are no higher than in other tissues nor does selective accumulation of barbiturate occur in subcortical loci. Barbiturates readily cross the placenta and are distributed throughout the tissues of the fetus. Although barbiturates appear in the cerebrospinal fluid, in concentrations as high as 0.250 mgm per cent in persons taking large amounts with suicidal intent, there is no correlation between the degree of depression and the barbiturate level (Kozelka and Tatum, 1937).

Full information concerning the fate of each individual barbiturate in man is not yet available. The body possesses two methods of eliminating the drugs, *i.e.* destruction in the liver and excretion through the kidneys. A few barbiturates are largely excreted; others are completely destroyed in the liver, and still others are partly excreted and partly destroyed. The fate of a particular barbiturate evidently depends on its chemical configuration but one cannot predict from chemical structure exactly how the drug will be handled by the body. In general, however, the thiobarbiturates and those with complex cyclic radicles such as evipal are less stable and almost completely destroyed in the liver. Barbiturates with short alkyl radicles are more apt to be stable and excreted in the urine.

Rôle of the Liver. Those barbiturates which are destroyed in the body undergo side-chain oxidation in the liver. The degradation products may appear in the urine, and as a rule have entirely lost their anesthetic potency, as shown for amytal, pentobarbital and ortal by Brundage and Gruber (1937). Destruction in the liver is the basis for the evanescent effects of the short-acting and ultra short-acting barbiturates. The importance of the liver in determining the duration of action and degree of depression resulting from a given dose of barbiturate has been demonstrated clinically and experimentally in a number of ways, all of which emphasize the necessity of knowing the fate of drugs in the body before one can give them with safety. For example, it has been reported that patients with impaired hepatic function have remained deeply anesthetized for many hours from a dose of evipal which in normal persons results in anesthesia for only fifteen minutes. Obviously, individuals with liver disease should not be anesthetized with barbiturates which depend for their intensity and duration of action on rapid destruction by the liver.

Similarly, Koppanyi and associates (1936) have shown that rabbits and cats, given pentobarbital and phenobarbital twenty-four hours after recovery from the effects of two hours of chloroform anesthesia, remain deeply depressed for long periods and may even die from doses which are only one-half the average fatal dose. Obviously, damage to the liver by chloroform prevents adequate detoxification of barbiturates. Furthermore, phenobarbital is a drug which also depends on the kidney for its excretion, but despite this alternative channel of elimination poisoning results when severe liver injury is present. Likewise, Pratt (1933) found that rabbits with livers injured by carbon tetrachloride or phosphorus, to the extent that bromsulfalein excretion was impaired, were very susceptible to the depressant action of pentobarbital, whereas the duration of action of barbital was not altered. Pentobarbital is almost completely destroyed by the liver in contrast to barbital which is largely excreted unchanged in the urine. Cameron and Saram (1938) verified this observation in rats with liver damage due to carbon tetrachloride by showing that the animals were more susceptible to the short-acting barbiturates—pentobarbital and evipal. When liver regeneration occurred, the susceptibility disappeared but if the pre-cirrhotic stage due to progressive liver damage was reached, the depressant action of the drugs was greatly enhanced.

Renal Excretion. Those barbiturates which escape destruction in the liver in smaller or greater degree are eliminated in the urine. Small amounts may appear in the milk after ingestion of large doses (Tyson and coworkers, 1938). Renal excretion occurs rather slowly, however, and this accounts for the longer duration of action of those members which are in good measure dependent on the kidneys for their elimination, such as barbital, phenobarbital, dial, ipral and alurate. After oral administration in man, from 65 to 80 per cent of barbital as such can be recovered in the urine, 30 per cent of dial, 25 per cent of phenobarbital and from three to eight per cent of amytal. Other barbiturates have not been adequately studied quantitatively in regard to their renal excretion.

The rather slow rate of excretion of barbiturates is the basis for the cumulative toxicity which occurs from their continued use. For example, in normal human beings, traces of barbital are still detectable in the urine nine days after ingestion of a hypnotic dose. Only eight per cent is eliminated in the urine in the first 12 hours, 20 per cent in 24 hours and 35 to 65 per cent in 48 hours.

When renal function is impaired, those barbiturates which depend upon the kidney for elimination may cause severe depression and poisoning. Thus it is important to know the status of renal function in order safely to prescribe a barbiturate. Argy, Linegar and Dille (1936), for example, have compared the excretion of barbital in normal and nephropathic subjects. Whereas nine normal individuals excreted an average of 14 per cent of 1.12 grams of barbital within 24 hours, eight nephropathic patients, given the same amount of drug, excreted an average of only six per cent. They noted in addition that barbital tended to cause oliguria in the latter group. The experiments of Hirschfelder and Haury (1933) on nephrectomized rabbits showed that barbital and phenobarbital, in particular, produce prolonged anesthesia and depression lasting until death whereas control rabbits recover in from 11 to 13 hours. Employing dogs, cats and rabbits with severe experimental nephrosis, Murphy and Koppanyi (1934) found that the animals did not recover from barbital and died in coma. Recovery did occur, however, from anesthesia produced by barbiturates less dependent than barbital upon the kidneys for elimination, such as pentobarbital, neonal, sandoptal and pernoston. Similarly, Gruber and Brundage (1937) found that nephrectomized dogs recovered as readily as did normal animals from anesthesia by ortal, a barbiturate which is destroyed by the liver. In a further study, Koppanyi, Murphy and Gray (1934) found that chickens eliminate barbital so slowly that they respond as do nephropathic mammals and die in coma from respiratory failure. They recover, however, from anesthesia produced by phenobarbital, pentobarbital, neonal and pernoston.

In *summary,* it may be stated that the ability of the liver to destroy barbiturates and of the kidney to excrete them determines both the duration of action and the toxicity of these compounds. Each member of the group is handled by the body in a distinctive manner, and the physician must know the fate and excretion of the drug he selects in order to employ it with safety. This is especially true when chronic medication is prescribed or when large doses are given parenterally.

Margin of Safety. For most groups of potent medicinals, the margin of safety is a major consideration in the selection of one drug in preference to another. However, it is highly problematical, whether significant differences in margins of safety exist between the various barbiturates. Some investigators, on the basis of experimental work on animals, are inclined to believe that there are detectable differences in therapeutic ratios among the barbituric acid derivatives. Others, however, do not agree with this opinion and believe that toxicity runs parallel to hypnotic potency. For example, it has been learned that, in order to produce a given degree of anesthesia in animals, the same percentage of the fatal dose had to be given regardless of the barbiturate selected. It must be granted that it is most difficult to measure small differences in grades of central depression in laboratory animals, and that the calculation of therapeutic ratio depends on the accuracy of such a measurement. It must also be conceded that the vast amount of clinical evidence available does not warrant the view that barbiturates differ from each other in margins of safety.

It would seem, therefore, that the doses of the various barbiturates required to produce sedative, hypnotic and anesthetic grades of depression bear a rather fixed relationship to the minimal fatal dose. Although the relation of chemical structure to pharmacological action is not always predictable, it would appear that attempts to obtain barbituric acid derivatives with appreciably higher margins of safety than those now available are not likely to meet with success, and that as more potent compounds are produced it will be found that their toxicities are also proportionately increased. The Council on Pharmacy and Chemistry has succinctly stated the prevailing opinion on this question as follows, ". . . there is no satisfactory evidence that the margin of safety between therapeutic and toxic doses of these (*barbituric acid*) derivatives is wider than in the case of barbital itself." In clinical practice, therefore, the physician need not at present be concerned about the therapeutic indices of the barbiturates but rather he should look to other factors for his selection, particularly the duration of action desired.

Choice and Classification of Preparations. A confusingly large number of barbiturates are available for clinical use. The safest guides to follow are the patient's requirements and the duration of action desired (Fitch and Tatum, 1932). Factors of idiosyncrasy and contraindication must be observed. It is urged that the physician become well acquainted with a few well-known and adequately studied barbiturates, particularly those included in the N.N.R., and use these as occasion demands rather than prescribe promiscuously each new compound that is placed on the market, often without sufficient experimental or clinical appraisal.

For clinical purposes, barbiturates may be classified into four main groups, depending upon their duration of action, as shown in Table 6. In general, speed of onset of hypnotic effects after oral administration and rapidity of recovery parallel the duration of somnifacient action.

TABLE 6

CLASSIFICATION OF BARBITURATES ON BASIS OF DURATION OF HYPNOTIC ACTION *

LONG-ACTING	MODERATE DURATION	SHORT-ACTING	ULTRASHORT-ACTING **
Alurate	Amytal	Evipal	Evipal
Barbital	Ortal	Seconal	Pentothal
Dial	Pentobarbital		Thio-ethamyl
Ipral	Pernoston		
Neonal	Phanodorn		
Nostal	Sandoptal		
Phenobarbital			

* Average soporific doses given orally.
** Anesthetic doses given intravenously.

Preparations and Doses. The barbiturates are odorless, white, crystalline powders which are slightly bitter to the taste, poorly soluble in cold water but soluble in alcohol and hot water. Saturated aqueous solutions are acid to litmus. The sodium salts are freely soluble in water and their solutions are alkaline to litmus. The barbiturates are marketed in tablet, capsule and suppository form, and can also be prescribed in solution. The N.F. contains an *Elixir of Barbital* (0.14 gram per four cc), and an *Elixir of Phenobarbital* (0.016 gram per four cc). These two elixirs are the only official solutions of barbiturates. Several of the sodium salts used for parenteral therapy are marketed as dry powders in sterile ampules, to which sterile water is added to effect solution before use, because of the instability of the sodium salts in aqueous solution.

The average adult *hypnotic* doses of the several barbiturates are given in Table 5. Many factors which determine the efficacy and safety of this average dose have already been discussed, and others will be described. The *sedative* dose is usually about one-third to one-fourth of the hypnotic dose, and may be repeated three or four times daily.

Barbiturate Poisoning. Poisoning by barbiturates may occur accidentally in the course of their therapeutic use or with suicidal intent. The wide and promiscuous sale of this class of sedatives provides ample opportunity for their employment in suicides. As Hambourger (1939) has pointed out, more than two million doses of barbiturates are sold daily in the United States. Suicide has its styles, and the use of hypnotic drugs, especially barbituric acid derivatives, is currently in vogue. The national incidence of suicide by means of barbiturates (1932–1936) is 4.2 per cent of that for all poisons (except gases), and the incidence in large cities ranges from two to 16 per cent. Accidental poisoning is especially likely to occur when the barbiturates are used for intravenous anesthesia by persons not sufficiently experienced in this highly specialized field. Occasionally, idiosyncrasy is the basis of the intoxication. Richards (1934) has reported three cases of acute barbiturate poisoning due to what he has called "automatism." Failure of the drug to produce sleep may cause a twilight zone during which the patient does not remember having already taken the medication and he may unwittingly ingest all the remaining tablets. An incorrect diagnosis of suicide may be given if death results from such accidental intoxication.

Death from ordinary therapeutic doses is practically unknown. In an examination of the pertinent literature by Gillespie (1934), no case was found on record in which either a single dose or repeated doses of average therapeutic size caused death in the absence of complicating factors. The rare cases of marked idiosyncrasy, such as fatal skin reactions, of course, are excluded. Severe poisoning usually occurs when an amount of barbiturate has been ingested which is five to 10 times the full oral hypnotic dose. The fatal dose varies with many factors and cannot be stated with certainty, but when over 15 times the ordinary hypnotic dose has been absorbed, it usually will prove extremely difficult to save the patient's life. The fatality rate in hospitalized cases of acute barbiturate poisoning is over seven per cent (Hambourger, 1940), and may rise to 15 per cent in severely poisoned cases.

Acute Poisoning. Symptoms and Signs. These are referable especially to the *nervous* and *cardiovascular* systems. When intoxication is fully developed, extreme lethargy, deep sleep or coma is characteristic. A period of excitement and delirium accompanied by hallucinations may occasionally precede the depression of the nervous system. Respiration is affected early, the respiratory rate is slow and the minute volume considerably decreased. Cheyne-Stokes rhythm may be present. Prolonged respiratory depression and the consequent anoxia adversely affect the cardiovascular system. The capillaries may dilate widely, become increasingly permeable and shock may result. Shallow respiration coupled with a low blood pressure favors the onset of hypostatic pneumonia. The activity of the reflexes conforms in a general way to the intensity of the central depression, but the deep reflexes are occasionally maintained for some time despite coexistent coma. The Babinski great toe reflex is often positive. The pupils react to light, as a rule, and are somewhat constricted, though at times they may be dilated. Occasionally, they are pin-point in size, as in morphine poisoning, and unresponsive to light.

The *blood pressure* does not fall until relatively late in the course of poisoning unless the drug has been injected intravenously in toxic amounts. Under this circumstance, the blood pressure falls rapidly to shock levels. After the oral ingestion of a barbiturate, however, the fall in blood pressure is due in large measure to the anoxia resulting from the decreased pulmonary ventilation. In severe grades of intoxication, direct depression of the vasomotor centers and a direct toxic inhibition of smooth muscle tone of smaller blood vessels also contribute to the hypotension. The pulse is rapid and weak.

As a result of the low blood pressure and possible central actions, *urine formation* is decreased or suppressed. This fact is of therapeutic importance because certain barbiturates cannot be detoxified and recovery from their effects is dependent upon adequate renal function. *Body temperature* falls and the *skin* is cold, moist and cyanotic.

The *diagnosis* of barbiturate poisoning is made from the history and physical examination, but differentiation from poisoning by other central nervous system depressants or from coma due to other causes may at times be difficult. Identification of the poison in the stomach contents or urine, or in the viscera after death may be required for medicolegal purposes, and fairly specific and quantitative methods for such identification are available (*see* Brundage and Gruber, 1937; Kozelka and Tatum, 1937; Kozelka, Nelson and Tatum, 1939; Delmonico and Adams, 1939).

The *prognosis* depends on the amount of and the particular barbiturate ingested, the general health of the patient, the type of therapy instituted and the interval elapsing between the ingestion of the poison and the beginning of treatment. The longer the patient survives, the better is his chance for ultimate recovery, and the prognosis is more favorable if the patient survives for 24 or 36 hours. Improvement may be noted within one hour after specific antidotal measures are employed, but the patient may not be out of danger for four days or longer if a long-acting barbiturate is the cause of poisoning (Figure 13).

Death, if it occurs early, is usually the result of paralysis of the respiratory center. The shorter-acting barbiturates are particularly prone to produce death from respiratory depression. If death is delayed, vasomotor collapse and hypostatic pneumonia frequently are the causes of the fatal issue. Bronchopneumonia may occur in a patient who has regained consciousness and apparently recovered, and therefore a guarded prognosis is advisable. The cerebral changes which occur in fatal cases of acute barbiturate poisoning consist of morphological alterations of ganglion cells in the brain, often associated with neuronophagia but without marked macroglial or microglial reactive phenomena. The changes are diffuse, but somewhat more marked in the medulla, especially the olivary bodies. The lesions are non-specific and resemble those produced experimentally by a variety of organic and inorganic poisons. More important and dangerous is the occurrence of cerebral edema with distention of the subarachnoid space and the cerebral tissue spaces (Hassin, 1939).

Therapy. If the barbiturate has been taken orally, which is usually the case, the stomach should be lavaged well with warm water by use of the gastric tube. Emetics are seldom efficacious and may further add to the depression. A solution of potassium permanganate (1:2000 to 1:5000) may be employed as a lavage medium if available, but is effective only for dial and alurate and not for the more commonly used barbiturates—barbital, phenobarbital and amytal (Hatcher, 1935). Magnesium sulfate, 20 to 40 grams, may be left in the stomach at the termination of the lavage in order to hasten the passage out of the bowel of the unabsorbed poison.

Attention should be focused without delay on the maintenance of adequate respiratory exchange and blood pressure, and lessening of the degree of central depression. If breathing is markedly depressed, *artificial respiration* may be needed, and a Drinker respirator may be life-saving. If breathing has ceased but the heart is still beating, *oxygen* is preferably delivered through a tracheal catheter, if this is possible. Drugs available for stimulation of the depressed respiratory center are *caffeine with sodium benzoate, ephedrine, coramine, metrazol, picrotoxin* and *strychnine.* Atropine is not very effective as a medullary stimulant. The caffeine salt may be given intramuscularly in the dose of 0.5 gram, every hour or two as needed. Enemas containing strong, warm black coffee are also helpful. Ephedrine may be injected intramuscularly in the dose of 10 to 30 mgm and repeated every hour or two if necessary. Both ephedrine and caffeine also lessen the degree of central depression by stimulation of higher cerebral centers, and ephedrine in addition has salutary effects on the cardiovascular system.

Strychnine and picrotoxin benefit the patient not only by stimulating respiration but also by lessening the degree of coma through their actions on higher centers and by stimulating the medullary vasomotor centers. Strychnine, in particular, also increases the reflex activity of the spinal cord and antagonizes barbiturates in this locus. Strychnine may be given intramuscularly in the dose of from two to 10 mgm and repeated approximately every two hours, depending upon the severity of the poisoning and the response of the patient. On occasion, it may be given intravenously when the patient is *in extremis.* Picrotoxin may be given as described elsewhere (page 264), but the status of this drug cannot be accurately stated. It is not fortified by the accumulated body of clinical and experimental evidence that exists for the use of other analeptics, and it is somewhat difficult to obtain. Dramatic results have nevertheless been reported from its use in barbiturate intoxication. Coramine and metrazol may be employed but the former, at least, is not as dependable as the agents hitherto mentioned. The inhalation of carbon dioxide and oxygen offers another measure for the stimulation of respiration.

In Figure 13 is illustrated the use of ephedrine and strychnine in the treatment of a patient who took 4.75 grams of phenobarbital in an attempt at suicide. It is evident from a study of the figure and its legend that the amount of ephedrine and strychnine given and the intervals and routes of administration employed were selected to meet the urgency of the case and were altered as the patient's condition improved. The use of large doses of ephedrine and strychnine in this case is again illustrative of the general principle that the level of functional activity of the nervous system determines the amount of central stimulant or depressant drug which may be given with safety.

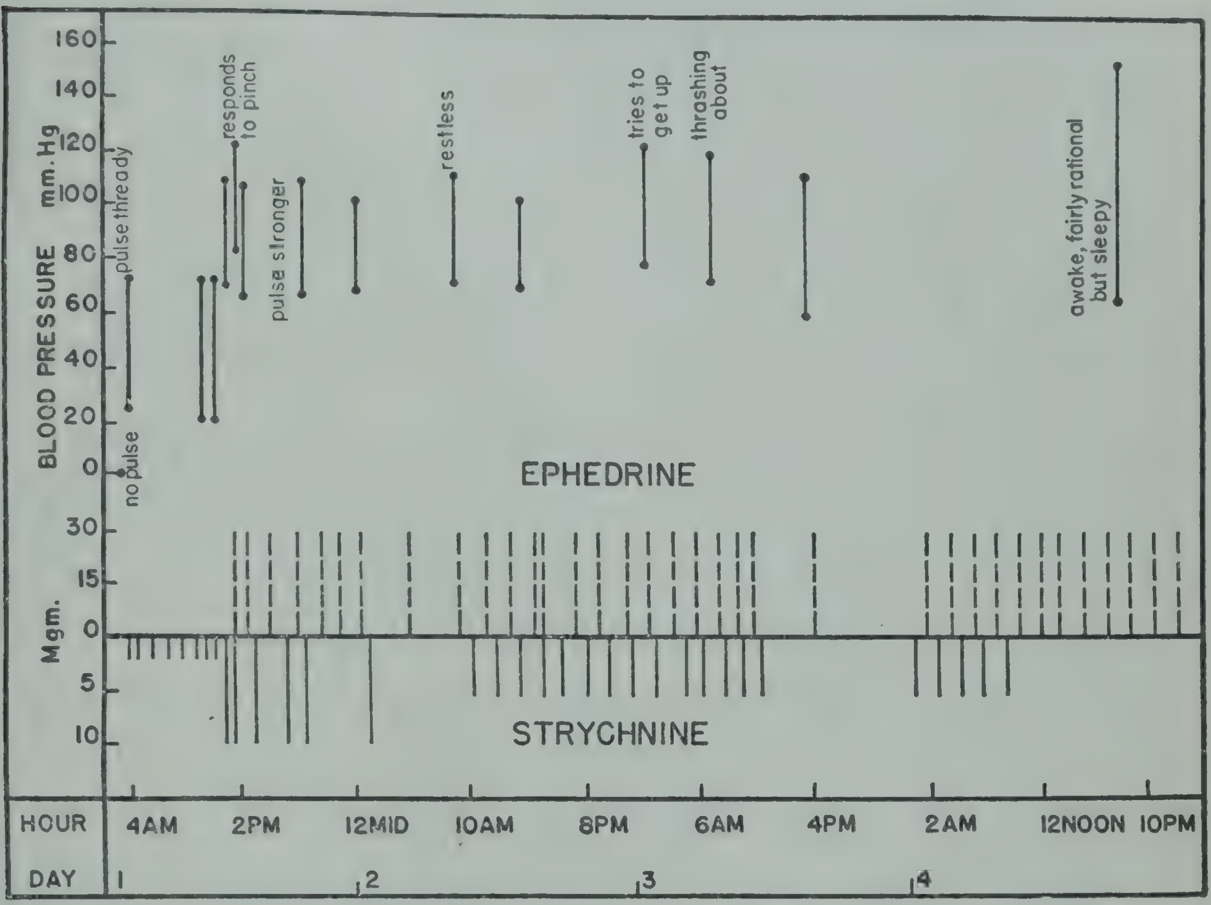


FIGURE 13. *Treatment of acute phenobarbital intoxication with strychnine and ephedrine.*

Female, aged 27. Six hours prior to hospital admission, the patient swallowed 4.75 grams of phenobarbital. Upon admission she was cyanotic and deeply comatose; respirations were shallow and slow; the pupils were "pin-point" and did not respond to light; there was no reaction to painful stimuli; the radial pulses were not palpable; the blood pressure was unobtainable and loud râles were heard over the lungs. Therapy with ephedrine sulfate intramuscularly and strychnine sulfate subcutaneously was instituted, intravenous injections being employed only for the first dose of ephedrine and for the first two 10.0 mgm doses of strychnine. Note that the doses and intervals employed were varied according to the patient's response, and that four days were required before antidotal medication could be terminated. The total amount of medication given over this period was 171 mgm of strychnine and 1200 mgm of ephedrine. Glucose and fluids were administered parenterally. (After Weiss, 1936. Courtesy of *International Clinics*.)

All the respiratory stimulants previously mentioned have a salutary effect on the cardiovascular system by improving pulmonary ventilation and relieving anoxia. In addition, most of them increase vasomotor tone by a central action. Ephedrine, in addition, has well-known peripheral effects on the heart and blood vessels which are of value in maintaining the blood pressure. If shock has intervened, however, reliance cannot be placed upon vasoconstrictor drugs and the measures outlined for the therapy of shock should be instituted. The intravenous use of a hypertonic solution of glucose, in particular, not only aids in maintenance of normal blood volume but promotes adequate urine formation and provides nourishment.

It is a matter of considerable importance whether diuresis hastens the excretion of a barbiturate and recovery from poisoning. The evidence available suggests that diuresis does neither. Nevertheless, adequate fluid intake should be maintained to insure optimal renal excretion, and if shock is present fluids of proper composition should be administered with the additional objective of restoring a normal blood volume. A five per cent solution of glucose in saline, saline hypodermoclysis and rectal drip may be employed for the administration of fluid and electrolyte to the comatose patient. Diuretic drugs are not indicated.

Additional measures in the treatment of acute barbiturate poisoning include keeping the patient warm, maintaining an adequate state of nutrition and preventing acidosis, careful nursing attention, and frequent changes in posture to prevent hypostatic pneumonia and decubitus ulcers.

Chronic Poisoning. Chronic poisoning may occur from the continued use of barbiturates in doses which allow for cumulative toxic effects. Thus, chronic poisoning is more apt to occur from the use of the longer-acting barbiturates. The syndrome is often bizarre and may offer a puzzling diagnostic problem unless the physician has a high level of suspicion for drug intoxication. If continued sedative effects are required, barbiturate medication should be alternated with hypnotics of a different chemical class.

Symptoms consist of drowsiness, a desire to sleep especially after meals, and slowness of thought, failing memory, incoherent speech, mental depression, confusion and disorientation. The more fully developed picture includes abnormal neurological findings as well as the mental phenomena mentioned. Vertigo, ataxia, nystagmus, diplopia, strabismus, difficulty of accommodation, dysarthria, paresis of the limbs, tremors, numbness and tingling, and increased, decreased or absent deep reflexes may occur. Many neurological syndromes may be closely simulated. In addition, gastro-intestinal disturbances occur and consist especially of anorexia, obstipation, foul breath and coated tongue. Skin rashes may develop. These may be erythematous, urticarial, purpuric or scarlatiniform in character. The rash caused by phenobarbital, in particular, may itch and it may resemble the exanthem of measles or of scarlet fever without the circumoral pallor. Pruritus is sometimes marked and the cutaneous lesions may be accompanied by fever. A rash may also appear on the tongue after prolonged use of phenobarbital. Rarely, exfoliative dermatitis may occur from phenobarbital and death may result (*see* Sweitzer and Laymon, 1937; Wile and Benson, 1940). The urine may contain albumin, casts, and occasionally hematoporphyrin; weight loss may be prominent, and anemia of the secondary type is not infrequent.

Treatment consists in stopping immediately all sources of ingestion of the offending agent and the institution of supportive and symptomatic therapy. Three weeks to a month may be required for the symptoms to clear, and recovery may be incomplete in elderly debilitated individuals. That a toxic effect on nerve cells may occur in chronic poisoning by barbiturates and account for the clinical picture is suggested by the delay in recovery and by the experimental work of Pickworth (1927), Seevers and Tatum (1931), and others. More definite evidence on this point is required, however, before the lesions which have been described can be accepted as specifically due to the chronic use of barbiturate, and some investigators have failed to find neurological lesions after prolonged administration of large doses of barbiturates in animals. The cause which prompted the patient to take the drug for a protracted period should be removed if possible.

Idiosyncrasy. Natural idiosyncrasy to the barbiturates usually manifests itself in the form of a *hangover,* excitement or pain. A hangover from relatively small hypnotic doses occurs especially in neurotic patients, particularly when the longer-acting barbiturates are employed. After the initial and characteristic period of depression has passed, lassitude, vertigo, nausea and vomiting, and diarrhea may be noted, and emotional disturbances and phobias may be accentuated. In some persons, barbiturates repeatedly produce excitement rather than depression, and the patient usually appears to be inebriated. Like other non-analgesic hypnotic drugs, the barbiturates when given in the presence of pain may cause restlessness, excitement and even delirium. Rarely the use of barbiturates results in localized or diffuse myalgic, neuralgic or arthritic pains especially in psychoneurotic patients with insomnia (Castin and Gardien, 1934; Weiss, 1936). Symptoms may be severe and last for days after the use of the drug is discontinued. The pains may appear in paroxysms, are most intense in the early morning hours, and are most frequently located in the region of the neck, shoulder girdle and upper limbs.

Acquired idiosyncrasy to the barbiturates consists chiefly of reactions which are allergic in nature, and occurs especially in persons who tend to have asthma, urticaria, angioneurotic edema, etc. Barbiturate-induced reactions in this category include localized swellings, particularly of the eyelids, cheeks or lips, erythematous dermatitis and bullous, cutaneous lesions. The reactions clear rapidly after cessation of the drug. There is abundant evidence that the barbiturates do not produce agranulocytosis, but they may be incorporated in patented nostrums which also contain aminopyrine, the agent most commonly causing agranulocytosis.

Contraindications. There are a number of contraindications to the use of barbiturates. They should not be prescribed for persons who manifest idiosyncrasy to them. For patients with impairment of renal function, those barbiturates which depend on renal excretion for their elimination should not be employed. The same holds true for individuals with impaired hepatic function with respect to barbiturates which depend on the liver for their destruction. It has been reported that phenobarbital aggravates the muscular rigidity accompanying Parkinson's disease to the extent that the patient may become bedridden (Ziskind and Ziskind, 1937). Confirmation of this observation, elucidation of the mechanism involved, and additional information concerning the other barbiturates are desirable.

Untoward responses attributable to the barbiturates are particularly likely to occur in patients with fever, hyperthyroidism, diabetes mellitus, severe anemia and congestive heart failure. However, none of these conditions represents an obligatory contraindication to the use of the barbiturates and excellent results are often obtained from their judicious administration.

Advantages of Barbiturates as Central Depressants. The barbiturates possess several advantages as depressants of the central nervous system, some of which are unique. Any degree of depression from the slightest sedation to deep surgical anesthesia can be obtained by a proper selection of drug, dose and route of administration, and the barbiturates lend themselves to a greater variety of uses than any other group of central depressants. The barbiturates can be administered by several routes, and their parenteral use provides definite advantages in emergencies. Given in large parenteral doses, these drugs have greater anticonvulsant properties than chloral hydrate or paraldehyde. Given intravenously, the ultra short-acting members are useful for producing surgical anesthesia of short duration. Phenobarbital has specific value in the symptomatic therapy of epilepsy. The barbiturates also are serviceable in protecting against the toxic effects of local anesthetics. Ordinary hypnotic doses have no untoward effects on vital functions of the body. Finally, the barbiturates are not disagreeable to the taste and can be dispensed in several forms for oral ingestion.

It should be noted, however, that the ease with which the barbiturates can be prescribed by the physician and taken by the patient is probably their greatest disadvantage in that they are often employed when other sedatives or other therapy might be preferable. Unfortunately such excellent hypnotics as chloral hydrate and paraldehyde have been considerably neglected since the barbiturates have become popular. Habituation probably is more readily developed to barbiturates than to chloral hydrate and paraldehyde due to the lack of any unpleasant taste or odor. It is highly to be desired that Federal or state laws be enacted to prevent the wide lay purchase and promiscuous use of barbiturates without physicians' authorization.

Therapeutic Uses

The barbiturates have numerous and important therapeutic uses. Most commonly, however, they are employed for their somnifacient and sedative actions.

Hypnosis. When administered for the purpose of inducing sleep, the barbiturates should be given at a time when their depressant effect will coincide with other factors promoting sleep. For example, from one-half to one hour is usually required for barbital and phenobarbital orally administered to be absorbed in sufficient amount to exert their initial action. From fifteen to thirty minutes are required for amytal and pentobarbital, and fifteen minutes or less for the short-acting drugs. It is important, therefore, that the patient be in bed and prepared for sleep in anticipation of this hypnotic effect. Natural dreamless sleep lasting from four to eight hours usually follows when the longer-acting drugs are used, and some lassitude may be noted upon awakening. The soporific effects of the short-acting members last only from two to four hours, and hangover is less frequent. If the patient experiences difficulty in falling asleep, the short-acting barbiturates may be selected. If, on the other hand, frequent awakening during the night is the chief complaint, the longer-acting drugs may be given. Some prefer to give the longer-acting barbiturates in two equal portions, the first dose two hours before bedtime and the second from one-half to one hour before retiring. This technic is calculated to prepare the patient for sleep by inducing drowsiness. The symptomatic relief obtained by the use of somnifacient drugs should not lessen the attempt to discover the causes of the insomnia or prevent the employment of the other reliable measures efficacious in this disorder. Repeated nightly use of barbiturates may result in habituation, and if hypnotic drugs are absolutely necessary over an extended period, medication with barbiturates should be alternated with the use of paraldehyde and chloral hydrate.

Sedation. For purposes of sedation, the barbiturates allow a wider range of therapeutic effects than is afforded by bromides. Sedation of any desired degree is obtainable within an hour or two, whereas bromide medication must be given approximately two days before its effects appear and the degree of sedation is difficult to regulate. Sedative doses of barbiturates are from one-third to one-fourth those used to induce sleep, and may be given three or four times daily, if necessary. Some of the more common conditions in which the sedative action of this class of drugs is desired include anxiety tension states, hyperthyroidism, essential hypertension, nausea or vomiting of functional origin, seasickness, acute labyrinthitis, pylorospasm in infants, chorea, cardiac failure, whooping cough, etc.

In hyperthyroid patients, the judicious use of barbiturates for sedation decreases muscular activity, lessens nervous excitability, and relieves worry. Care should be observed, however, because thyrotoxic individuals occasionally react poorly to barbiturates. The sedative action of these compounds is also of value in overcoming the central stimulating effects of ephedrine and benzedrine. The latter agents may thus be employed for their sympathomimetic effects or in myasthenia gravis without undue central excitation or insomnia resulting from con tinued medication.

In acute maniacal states and particularly in delirium tremens, the barbiturates are of value and it may be necessary to employ them in hypnotic or even anesthetic doses by the parenteral route. The sedative action of barbiturates is also helpful in the management of drug addicts undergoing withdrawal therapy. The prolonged use of barbiturates for sedation in patients with psychiatric disorders may result in confusion and accentuation of symptoms, and should be avoided. Although the barbiturates have been recommended to prevent nausea and vomiting in patients undergoing deep x-ray or radium therapy, their use may precipitate a toxicoderma due perhaps to cutaneous sensitization as a result of porphyrinemia. The lesion may be mistaken for roentgen erythema.

Potentiation of Analgesia. The potentiation by barbiturates of the analgesic action of the salicylate, pyrazolon and paraminophenol derivatives has been discussed. For combination with analgesics, the shorter-acting members are particularly suited. A large number of proprietary nostrums on the market for the relief of pain consist of just such a combination of drugs. The use of patented drug mixtures of secret composition or even of more legitimately marketed preparations containing fixed doses of ingredients can only be condemned. The physician can easily prescribe drugs of his own selection in such amounts as will best meet the changing needs of his patient. When the barbiturates are given in conjunction with analgesics, only about one-third of the hypnotic dose should be prescribed.

The barbiturates alone, in doses which do not cause unconsciousness, do not produce analgesia and they cannot be expected to induce sedation or sleep in the presence of pain. The barbiturates have been reported to give relief to a few patients suffering from syphilitic gastric crises or from migraine but such cases are exceptional.

Anticonvulsant Uses. The barbiturates are of great value in the symptomatic control of convulsions, such as occur in *tetanus, eclampsia, status epilepticus* and *cerebral hemorrhage.* They are also effective in combating convulsions caused by *cocaine, strychnine,* and *picrotoxin,* and those occurring during *general anesthesia.* The barbiturates with moderate or short duration of action are usually selected and are given intravenously if necessary. The amount injected is much more important than the particular barbiturate employed. Only enough should be administered to control the seizures, because when the convulsions cease the patient may sink into a deep coma if more barbiturate than absolutely necessary has been given. Usual doses for intravenous administration are sodium phenobarbital, 0.3 to 0.7 gram, sodium pentobarbital, 0.3 to 0.5 gram, and sodium amytal, 0.4 to 0.8 gram. The injection should be made slowly (30 to 60 mgm per minute), and the respirations and degree of muscular relaxation carefully noted. The drug may be repeated in amounts and at intervals determined by the patient's condition and response to therapy.

Prophylaxis Against Local Anesthetics. The specific value of the longer-acting barbiturates in the prevention of toxic reactions from cocaine and the synthetic local anesthetics is well established, and is fully discussed elsewhere (page 304). Should excitement or convulsive phenomena occur as a result of the local anesthetics, solutions of soluble barbiturates should be injected parenterally as described.

Control of Epilepsy. Phenobarbital was introduced for the symptomatic control of epilepsy by Hauptmann in 1912, and it is the only member of the barbiturate group effective for this purpose. Phenobarbital has advantages over bromides in that its action starts within an hour or two after ingestion, that it can be used for the control of acute or severe attacks, and that its use is not followed by the fetid breath, skin rash and sluggishness which frequently accompany bromide medication. Effective doses of phenobarbital, however, produce some measure of central depression and the drug is thus inferior in this respect to dilantin.

The adult dose of phenobarbital for the control of epilepsy varies considerably, but averages between 0.1 and 0.13 gram daily. This may be given in divided doses or the entire amount may be given before retiring, if nocturnal epilepsy exists, or in the morning for the diurnal form. Most failures are due to unsatisfactory regulation of the dose. The necessity for careful adjustment of dosage and the fact that very large amounts may be required by some individuals are emphasized by Lynch (1939) who reports a series of 116 epileptic patients in whom excellent results were obtained with phenobarbital. Doses of phenobarbital as large as 0.3 to 0.6 gram daily occasionally may be required to control seizures (Cohen and coworkers, 1940; Lennox, 1940). If these large doses cause drowsiness, dizziness and ataxia, such toxic effects may be dissipated by the concomitant administration of benzedrine (five to 25 mgm daily). This allows larger doses of phenobarbital to be employed than would otherwise be possible and the benzedrine apparently has no untoward effect on the incidence or character of the seizures (Ebaugh, 1940; Cohen and associates, 1940). Some patients may require medication for only five days of every week, thus decreasing the possibility of cumulative toxic effects. If for any reason the drug is discontinued, phenobarbital should never be stopped abruptly, because severe seizures or status epilepticus may result. The patient or his guardian should be warned concerning this point. If bromide or dilantin is being substituted, the dose of phenobarbital should be decreased gradually over a period of three or four days until the bromide or dilantin has had an opportunity to exert its effects. Medication should be continued until one or two years of freedom from seizures have elapsed, after which the dose may be decreased or even cautiously omitted.

The results obtained with phenobarbital are superior, in general, to those with bromide, although reports vary in this regard. Lennox (1940) states that of 766 noninstitutionalized epileptic patients receiving phenobarbital, 65 per cent were improved with respect to seizures and 30 per cent with respect to mentality; of 289 similar patients taking bromides, 53 per cent reported improvement regarding seizures, and 26 per cent regarding mentality. Grand mal responds better than does petit mal. Both the severity and frequency of seizures are decreased and the mental and physical well-being of the patient is correspondingly improved. Therapy, of course, is purely symptomatic. Careful psychological tests show that deterioration of the intellect does not occur as a result of medication with phenobarbital (Somerfeld-Ziskind and Ziskind, 1940).

Optimal doses of phenobarbital may be employed in conjunction with dilantin. The study of Cohen and collaborators (1940) appears to indicate that a striking synergism exists when phenobarbital and dilantin are used together, the combination being far more efficient in reducing the incidence of seizures than is either drug alone. Phenobarbital may also be administered together with a ketogenic diet, thus allowing the latter to be modified to a sufficient extent to make it more palatable.

Phenobarbital is less effective for petit mal and may, in large doses, make psychic seizures worse. Overdosage may cause symptoms resembling the mental or behavioral characteristics of psychic epilepsy. The investigations of Lennox and associates (1936, *et seq.*) have revealed that the abnormal electrical patterns, obtained with the electro-encephalograph, characteristic of petit mal are inhibited by phenobarbital or prevented from continuing sufficiently long to constitute a clinical seizure. According to these workers (*see* Lennox, 1940), epilepsy is a paroxysmal cerebral dysrhythmia. The rate of electrical waves recordable from the brain in grand mal is abnormally fast, in psychic seizures abnormally slow and in petit mal alternately fast and slow. Phenobarbital tends to slow the rate and hence is principally useful in grand mal and may aggravate psychic epilepsy. The actions of phenobarbital on the motor cortex, which may further explain the basis for the efficacy of the drug in epilepsy, have already been described (page 131).

A number of patients and even physicians have come to attach special virtue to the name "luminal" in the treatment of epilepsy. "Luminal" is merely a copyrighted trade name for a particular brand of U.S.P. phenobarbital. The drug possesses no special merit and its cost is much greater than that of the official preparation. The desirability of prescribing official drugs rather than expensive proprietary preparations cannot be too greatly stressed.

The use of drugs, including phenobarbital, in the therapy of epilepsy has been authoritatively reviewed by Lennox (1940).

Uses in Anesthesia. The barbiturates have a number of uses in anesthesia, including their employment for general anesthesia, basal anesthesia, preanesthetic medication and obstetrical amnesia.

(1) *General Anesthesia.* For selected surgical operations of brief duration, the ultra short-acting barbiturates may be employed for intravenous anesthesia provided the anesthetist or surgeon is adequately trained in this field. For example, intravenous anesthesia by barbiturates has been found of value for changing painful dressings and removal of sutures, encephalography, procedures of short duration in the oral cavity, brief manipulations of simple fractures, treatment of accidental wounds, etc. It is also of prognostic assistance in determining the result to be expected from neurosurgical intervention in patients with hypertension, Raynaud's disease, etc. The preparations employed are the thiobarbiturates and evipal (Table 5). The technic and dangers of intravenous anesthesia have been described. The procedure is especially contraindicated in patients with cirrhosis of the liver, jaundice, shock, hypotension, asthma, pulmonary disease and marked debilitation. Atropine or scopolamine should be administered before-

hand to diminish untoward respiratory reflexes and prevent spastic adduction of the vocal cords.

(2) *Basal Anesthesia.* The barbiturates may be employed prior to inhalation anesthesia in doses sufficient to cause basal anesthesia. The technic, advantages and uses of basal anesthesia have been described elsewhere. The oral or rectal route rather than the parenteral route is employed, and the amount administered is from two to four times the ordinary hypnotic dose. Larger doses should not be employed for the greater the part contributed by the barbiturate to the anesthesia, the more prominent are the many disadvantages manifested by nonvolatile anesthetics.

(3) *Preanesthetic Medication.* The barbiturates in combination with atropine or scopolamine are widely employed for preanesthetic medication, usually in place of morphine. The oral route is used and the dose is intermediate between the hypnotic dose and that for basal anesthesia. More frequently, one of the longer-acting members is administered the evening before operation in order to insure sleep. Some anesthetists combine morphine and barbiturates but this enhances the danger of respiratory depression. Others give a hypnotic dose of a barbiturate orally two hours before inhalation anesthesia and then inject the usual doses of morphine and atropine one hour later. When local anesthesia is used, preanesthetic medication with barbiturates not only allows tranquillity but also provides specific protection against toxic reactions from local anesthetics.

(4) *Obstetrical Amnesia.* The barbiturates are employed in obstetrics with the objective of rendering the patient tranquil and drowsy so that she will sleep between pains and not remember the ordeal, but nevertheless remain sufficiently conscious to assist in the delivery. Some obstetricians administer enough barbiturate to obtain partial anesthesia and analgesic effects, while others shun their use entirely, claiming that they are as prone to depress the fetal respiratory center as is morphine. For example, despite the favorable results reported for the use of pentobarbital in combination with various other agents in labor, approximately one-third of the babies in some series do not breathe immediately, whereas less than two per cent is the normal figure when no anesthesia is employed. Respiration in the newborn, however, is retarded by all central depressants given to the mother, and even when nitrous oxide is the only agent used, 20 per cent of the infants do not breathe immediately. Indeed, it is believed by some investigators that the main factor responsible for the large number of asphyxiated babies at birth is not the employment of analgesic-amnesic drug combinations (except for morphine) but rather the low concentration of oxygen used with nitrous oxide during the second stage of labor (*see* Clifford and Irving, 1937). The respiratory mechanism of the mother may also be affected adversely by the use of barbiturates, and from studies on the effects of these agents on normal parturient women, Sheldon (1939) has concluded that doses producing more than sedation during labor should not be employed. The barbiturates are frequently combined with morphine, scopolamine, paraldehyde, and volatile anesthetics. The details of this important and complex subject cannot be further discussed. The use of barbiturates in obstetrical analgesia should be entrusted to experts in this field.

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CHAPTER 10

HYPNOTICS AND SEDATIVES

II. THE BROMIDES AND DILANTIN

THE BROMIDES

Historical. The element bromine was discovered in 1826 by Balard in the waters of the Mediterranean Sea at Montpellier, and nine years later the potassium salt of this element was introduced into the British Pharmacopeia for the treatment of splenomegaly. It was not recognized for some time that the bromide ion acted as a depressant of the central nervous system, and bromide salts were first used as a substitute for iodides in the therapy of scrofula, the close chemical relationship between the two elements having been recognized. Although no beneficial results were obtained, it was observed that administration of the bromide salts caused sedation. Inasmuch as potassium bromide was the preparation then employed, the depressant effect was attributed to the potassium ion, because intravenously administered potassium had been observed in the laboratory to cause depression and it was not realized that the oral ingestion of the cation could not possibly elevate the blood potassium sufficiently to duplicate experimental results obtained by its intravenous injection. If bromide had been employed in the form of its sodium salt, the pharmacological properties of the ion might have been recognized much earlier. By 1850, the actions of bromide on the nervous system were beginning to be recognized and in that year Huette published the first report of bromide intoxication. Bromide therapy of epilepsy apparently was recommended first by Sir Charles Locock in 1857. His reasoning was as follows: an unnamed person had tried potassium bromide on himself and found it to act as an anaphrodisiac, and since many cases of epilepsy were then thought to be caused by onanism, bromide should be used for epilepsy (quoted by Putnam, 1939). Locock employed the drug in fourteen cases with good results in all but one.

The typical central nervous system depression which results from the administration of the salts of bromine is now recognized as due to the bromide ion *per se*, and the particular cation to which it is linked does not influence this depressant action. It is likewise firmly established that only ionic bromide is active and bromine-containing compounds which do not release the element in ionic form (bromalhydrate, bromural, bromates, bromoform, etc.) do not share the action typical of the inorganic ionizable salts. Nevertheless, the basic mechanism of action of the bromide ion is obscure, some believing that the ion itself possesses central depressant properties and others contending that bromides act on the nervous system only by reducing the concentration of chloride ions, which are displaced by bromide.

Chemical Properties. All the inorganic salts of bromine which are employed clinically are very soluble in water, and moderately soluble in alcohol with the exception of the potassium salt. They are white crystalline powders which are saline to the taste. The chemical properties of bromides are well known and require no further discussion.

Laboratory Identification of Blood Bromides. The laboratory examination of body fluids, especially serum, for bromide is an extremely important procedure in the diagnosis of bromide intoxication, and the clinical recognition of this syndrome has been greatly facilitated by the advent of relatively simple chemical tests for bromide which can be conducted in the physician's office (Wuth, 1927; Diethelm, 1930; Hanes and Yates, 1938). The intensity of the reddish-brown color which develops when a solution of gold chloride is added to protein-free serum is an index of the amount of bromide present, and quantitative readings can be made against a standard in a colorimeter or by the use of a commercial comparometer. The significance of the height of the blood bromide level and the desirability under certain circumstances of routine examination of the serum for bromide will be discussed.

Pharmacological Actions. The only therapeutically useful property of the bromide ion is the depression of the central nervous system which it causes. Other effects of the ion in the body, such as those on the skin, mucosa and glandular secretions, are more correctly viewed as undesirable toxic side-effects.

Central Nervous System. The typical action of the bromide ion on the central nervous system is one of depression.Ordinarily, this action is controlled so as not to pass beyond a state of moderate sedation, but in large doses or with continued medication the bromides can cause marked depression of the cerebrospinal axis, even to the point of deep coma. In this respect the bromides share many of the actions of the depressant drugs of the hydrocarbon anesthetic series. Other tissues of the body react no differently to bromide than to chloride and are unaffected by concentrations of bromide which definitely alter functions of the nervous system.

In proper doses, the bromides cause mental calmness, sedation, drowsiness and sleep, if extraneous stimuli are minimal. Sleep induced by bromide medication is neither as deep nor as refreshing as that produced by the barbiturates, chloral hydrate or paraldehyde, and there may be a *hangover*. With larger amounts, lassitude becomes marked, intellectual processes are disturbed, thought and speech impaired, perception dulled and memory faulty. Still larger doses cause motor incoordination, lethargy, marked confusion and disorientation, delirium or stupor and then coma.

The early and empirical use of bromides for the control of the convulsive seizures of epilepsy focused attention on the action of bromides on the motor cortex. Albertoni, as long ago as 1882, demonstrated, by means of experiments on dogs, that adequate amounts of bromide could antagonize the effects on the motor cortex of direct electrical stimulation or convulsant agents. Neither bromide nor phenobarbital, however, is as selectively depressant to the motor cortex in epileptics as is dilantin. Merritt and Putnam (1938), for example, found that an amount of sodium bromide sufficient to prevent a cat from walking, elevated the convulsive threshold to electrical stimuli only about 50 per cent. An equivalent dose of phenobarbital trebled or quadrupled the threshold of excitation, but an amount of dilantin which increased the threshold to a similar extent caused no appreciable depression of other functions of the nervous system (Figure 15).

Mechanism of Action of Bromides. The mechanism of action of bromides on nerve cells is somewhat obscure. The tissue cells of the body, with the exception of the chloride-containing red blood corpuscles, are impermeable to both bromide and chloride. Therefore, the bromide ion must exert its pharmacological effects due to its presence in the extracellular fluids of the body, and nerve cells are apparently peculiarly sensitive to the substitution of bromide for chloride in their extracellular environment. Other tissues are relatively indifferent to the presence of bromide. For example, the chloride of the perfusion fluid of isolated hearts or other organs may be completely replaced by bromide without demonstrably harmful effects. The selective response of the cells of the brain to the bromide ion is unexplained.

The suggestion has been made that it is not the bromide ion in itself which depresses the functional activity of the cerebrospinal axis, but rather central depression results from the decrease in the concentration of the chloride ion which is displaced by bromide in the extracellular fluid. Unfortunately, it is almost impossible to obtain evidence on this point because as the bromide concentration rises, the chloride content of the extracellular fluids falls proportionately, the total electrolyte concentration remaining constant. A fall in the chloride content of the blood unassociated with bromide administration, however, does not produce typical central depression and for this reason it is believed that the bromide ion as such is the pharmacologically active agent in causing depression of the nervous system. Indeed, Hiatt (1939) has observed that the replacement of 50 per cent of the body chlorides by nitrate in dogs caused no observable changes in behavior.

Absorption, Distribution and Excretion. *Absorption.* The bromides are rapidly absorbed from the intestinal tract in a manner similar to chlorides. A high concentration of salts of bromine in the stomach may result in gastric distress and occasionally vomiting, due to local irritation caused by hypertonic solutions. For optimal absorption, therefore, bromides should be administered with sufficient water and preferably after meals.

Distribution. The bromides are distributed in the body in a manner almost exactly similar to chlorides. Thus the halogen can be found in all extracellular body fluids, secretions and transudates. Like chloride, bromide does not penetrate cell membranes. The exception is the red blood corpuscles, which are permeable to both chlorides and bromides. The concentration of bromide in erythrocytes is probably the same as in the serum (Palmer and Clarke, 1932; Van Dyke and Hastings, 1931). It is well known that the concentration of chlorides in body fluids remains quite constant under normal circumstances, and in man the average level of this anion in serum is approximately 355 mgm per cent (100 mEq). Inasmuch as the tissues of the body and the excretory organs do not distinguish between chloride and bromide, the administration of bromide results in the same adjustments as would occur if chloride had been given, that is, the total content of halogen in the extracellular fluid is kept at its normal value. When bromide and chloride constitute the halogen content of the body fluids, it is clear that their concentration ratio depends on the intake of each ion. Bromide displaces chloride during periods of bromide administration, and serious depletion of chloride may occur.

The bromide content of tissues and extracellular fluid has been studied especially by Mason (1936), Wallace and Brodie (1939), Smith and Walker (1938) and Weir and Hastings (1939). The ratio of bromide to chloride in the extracellular fluid of the tissues has been found to be the same as that existing in the serum. The ratio of bromide to chloride in the brain and cerebrospinal fluid, however, was found by Brodie and Wallace and by Weir and Hastings to be lower than that of the serum. It may be that equilibrium between the blood and the extracellular fluids of the nervous system occurs somewhat more slowly, thus giving a lower bromide content. It is possible that the cerebrospinal fluid is not in a simple physicochemical equilibrium with the blood and that this accounts for the lower bromide content of fluids of the nervous system.

Excretion. Bromides are excreted in the same manner as chlorides and thus almost exclusively in the urine. The kidney makes little distinction between the two halogens but rather functions to maintain the total halogen content of the extracellular fluids at a normal value. Bromides are therefore eliminated slowly. This can readily be appreciated from the consideration of what happens when one gram of sodium bromide is ingested. The kidneys will eliminate one gram of halogen-containing salt, the bromide to chloride ratio of the excreted salt being almost exactly that which exists in the serum. Inasmuch as the bromide content of the serum after a gram dose of sodium bromide is very low, much chloride and little bromide will be eliminated. If no more bromide is ingested, it will take many weeks before the ion is fully eliminated. If bromide medication is continued, the ion accumulates in the extracellular fluids until an equilibrium is reached, that is, until as much is excreted each day as is absorbed from the intestine. A patient receiving about six grams of bromide daily will reach equilibrium in approximately two weeks, depending on such factors as the chloride content of the diet, renal function, etc. Naturally, the lower the chloride intake the more rapid is the accumulation of bromide in the body for under such a circumstance the urinary excretion of halogen is minimal. Conversely, if the ingestion of chlorides is increased, the excretion of bromide is hastened, a fact which forms the basis for the therapy of bromide intoxication.

The ratio of bromide to chloride in the urine is not exactly the same as that in the serum, the kidney preferentially excreting chlorides (Hastings and coworkers, 1932; Mason, 1936). However, this preference is not marked and for practical purposes may be disregarded. Indeed, it has been denied that a preferential excretion of chloride occurs.

Small amounts of bromide appear in all secretions of the body. The tears, sweat, bile, milk, saliva and gastric juice thus contain the ion. The gastric juice of a patient receiving bromide medication contains hydrobromic acid, the acid-secreting cells of the mucosa of the stomach forming it from the bromide of extracellular fluid in a manner exactly similar to that for hydrochloric acid. The gastric mucosa secretes bromide somewhat preferentially over chloride, however, but this is not marked. In the alkaline juices of the duodenum, the hydrobromic acid is neutralized and the bromide is reabsorbed as the sodium salt. Bromides also cross the placental barrier with great ease, and the urine of infants born from mothers receiving bromide contains the ion.

Bromide Poisoning. *Acute.* Acute bromide intoxication is rare because amounts of the drug sufficiently large to elevate the serum bromide to a toxic level can hardly be ingested and retained without vomiting. Acute fatalities in man are thus unknown. However, in animal experiments the phenomenon is demonstrable and death occurs from respiratory failure and circulatory collapse.

Chronic Bromide Intoxication. Incidence. Poisoning from the continued use of bromides is known as *bromism.* The attention of physicians in the United States was first called to the high incidence of this condition by the publication of Wuth (1927). Despite the numerous papers subsequently appearing in the medical literature (Diethelm, 1930; Wainwright, 1933; Levin, 1933; Preu, Romano and Brown, 1936; Hanes and Yates, 1938; Curran, 1938; Gundry, 1939), chronic bromide intoxication occurs far too frequently. For example, from two to 10 per cent of the patients routinely admitted to psychopathic hospitals are found to be suffering from some degree of bromide intoxication. Of 238 routine admissions to the Phipps Psychiatric Institute at the Johns Hopkins Hospital, Wuth (1927) found 50 patients with bromide in their blood and 20 of these (nine per cent) showed signs of bromide intoxication. In 1000 consecutive cases admitted to the Colorado Psychopathic Hospital, Wagner and Bunbury (1930) recorded that 77 patients had blood bromide levels over 75 mgm per cent, and that in 44 of these the mental symptoms were due to or increased by bromide. Preu, Romano and Brown (1936) reported that 2.7 per cent of the patients admitted to the Psychiatric Clinic at the New Haven Hospital during 1935 showed signs of definite intoxication with bromide, and Preu (1939) later stated that 15 cases of *severe* bromide poisoning, including two deaths, were seen in 1800 consecutive admissions to the psychiatric service of the same hospital. Hanes and Yates (1938) state that approximately five per cent of admissions to psychiatric institutions are cases resulting from readily curable bromide intoxication. Most cases of chronic bromide poisoning admitted to psychiatric hospitals have been incorrectly diagnosed, and the reported incidence of bromide poisoning becomes higher as methods for testing the serum for bromides are adopted as a routine procedure. Neuropsychiatric patients should have routine blood bromide determinations.

There are several reasons why bromide intoxication occurs frequently. A physician's prescription is unnecessary in order to obtain the drug. A large number of nostrums which contain bromide do not reveal, by their trade names, the content of halogen. Many of these pass under the guise of "nerve tonics" and it is not unusual for patients to continue to take these patent medicines for the relief of the very symptoms of bromide intoxication which they produce. Finally, some physicians fail to appreciate that the continued use of bromides carries with it the definite possibility of cumulative poisoning, and that bromide is not always the benign, mild sedative which tradition would lead one to believe.

Symptoms. Symptoms of bromism may appear slowly or rather suddenly in the course of chronic bromide medication. Signs and symptoms are referable to the skin, glandular secretions, gastro-intestinal tract and nervous system. *Dermatitis* is common and is known as *bromide rash.* It starts most often as an acneform eruption on the face and at the hair roots, and may spread over the neck, chest and arms to involve the entire body. The dermatitis is occasionally indistinguishable from acne vulgaris. Severe skin lesions may appear in the absence of mental or neurological evidence of bromism, and the converse is also true. Indeed, only 25 per cent of the patients with bromism have cutaneous eruptions. Therefore, it is not necessary to have a bromide rash in order to have bromide poisoning, and a frank symptomatic psychosis due to bromide may remain undiagnosed unless this point is appreciated. The lesions of the skin may take unusual forms. A nodular type of lesion on the legs, known as nodose bromoderma, may be mistaken for tertiary syphilis and may develop into a sarcoma-like lesion. Pemphigus-like vesicles may appear and contain bromide in their exudate. Pustular lesions and ulcerations sometimes develop. Rarely, a bromide rash may appear on the tongue and hard palate.

The cause of the cutaneous eruptions is unknown. It has been claimed that the secretion of bromide in the sweat is the etiological factor and the unlikely suggestion has even been made that free bromine is perhaps split off in minute amounts in the acid sweat. However, it has been contended that the bromide rash begins in the papillary layer of the skin and not in the sweat glands which are involved only secondarily. The dermatitis may develop when the blood bromide level is still relatively low and, conversely, the skin may be clear despite the existence of high blood levels of bromide. It is said that persons with a seborrheic tendency have a predisposition to bromide acne.

Glandular secretions of the body are also affected in bromide intoxication. Excessive lacrimation and a mild conjunctivitis, resembling an acute coryza, may occur, as well as increased mucus secretion of the respiratory passages. These features are suggestive of the picture seen in iodism, but are not as marked as after iodide medication. The stimulation of the glands of the orbit, nose and broncho-respiratory tree may be due to the presence of bromide in their secretions.

Gastro-intestinal disturbances are sometimes prominent and are manifested by anorexia, foul breath, heavily furred tongue, sordes, constipation and gastric distress. The presence of hydrobromic acid in the gastric juice has already been mentioned, and may contribute to the gastro-intestinal symptoms. The lack of adequate intake of food and water results in rapid emaciation and dehydration. Low grade fever may also occur.

Mental and neurological disturbances are the most prominent features in bromide intoxication, and represent the most serious aspect of the syndrome. The signs and symptoms vary greatly from patient to patient, dependent upon constitutional and personality factors, and may take many bizarre forms, simulating closely almost every type of organic or functional mental or neurological disease. The earliest *mental symptoms* represent an extension of the therapeutic sedative action of the bromides, and consist of impaired thought and memory, drowsiness, disturbed consciousness with disorientation and emotional disturbances. In more severe cases. delirium, delusions, vivid auditory or visual hallucinations, violent mania, lethargy and coma may occur. The term "bromide psychosis" has arisen due to the frequency with which a symptomatic psychosis occurs in patients with bromide poisoning.

Neurological disturbances are also common, and are manifested in tremors of the hands, lips and tongue, speech defects, weakness, sluggishness of movement, motor incoordination, faulty gait, ataxia, increased, decreased or absent deep reflexes, positive Babinski great toe sign, decreased or absent superficial reflexes, especially of the mucous membranes, etc. The cerebrospinal fluid pressure may be elevated and in cases of severe intoxication papilledema may be present. The syndrome may simulate and has been mistaken for acute alcoholic intoxication, general paresis, tabes dorsalis, encephalitis, cerebral tumor, multiple sclerosis, uremia, and other entities. In the diagnosis of any bizarre nervous or mental disease, the physician should be suspicious that drug intoxication may exist, and bromides should be placed high in the list of possibilities. Patients suffering from depression, arteriosclerosis and fever are particularly likely to develop bromide psychosis from doses of the drug which do not appear excessive. Only by examination of the serum for its bromide content can the possibility of bromide poisoning be ruled out.

Correlation of Blood Bromide Levels and Symptoms of Bromide Intoxication. Bromide displaces chloride in the extracellular fluids ion for ion. The atomic weight of bromine (approximately 80) is about 2.3 times that of chlorine (approximately 35.5). The chloride content of the extracellular fluids of man is quite constant at 355 mgm per cent (100 mEq). If this value is reduced by replacement with bromides to the extent of 40 per cent, that is, from 355 mgm per cent to 213 mgm per cent (100 mEq to 60 mEq), extremely severe bromide intoxication is present and life may be seriously endangered. At this point, the blood bromide level would be 326 mgm per cent (40 mEq) $(142 \times {}^{80}/_{35.5})$.

There is no absolute correlation between the severity of bromide poisoning and the level of bromide in the blood. Many factors are concerned in determining whether a patient with a given level of blood bromide will show evidence of intoxication, among these being the general physical condition of the patient, the food and salt intake, the presence or absence of dehydration, vomiting, diarrhea and impaired renal function, the mental state, etc. For example, a patient who is cachectic, dehydrated and on a poor chloride intake may show severe symptoms of bromide intoxication when the blood bromides are only 100 mgm per cent (12.5 mEq), that is, when only 12.5 per cent of the blood chlorides have been replaced by bromide. Again, epileptic patients, who are properly managed, may continuously have blood bromide levels of from 100 to 125 mgm per cent (12.5 to 16 mEq) and note only mild sedation. However, the definitely "toxic zone" must be placed at blood bromide levels of 150 to 200 mgm per cent (19 to 25 mEq), and most patients with the latter concentration will show unmistakable evidence of poisoning. Indeed, extremely severe bromide psychosis has repeatedly been reported at this level. Bromide concentrations in the serum as high as 400 mgm per cent (50 mEq) have occurred, but these unusually high levels are not long compatible with life.

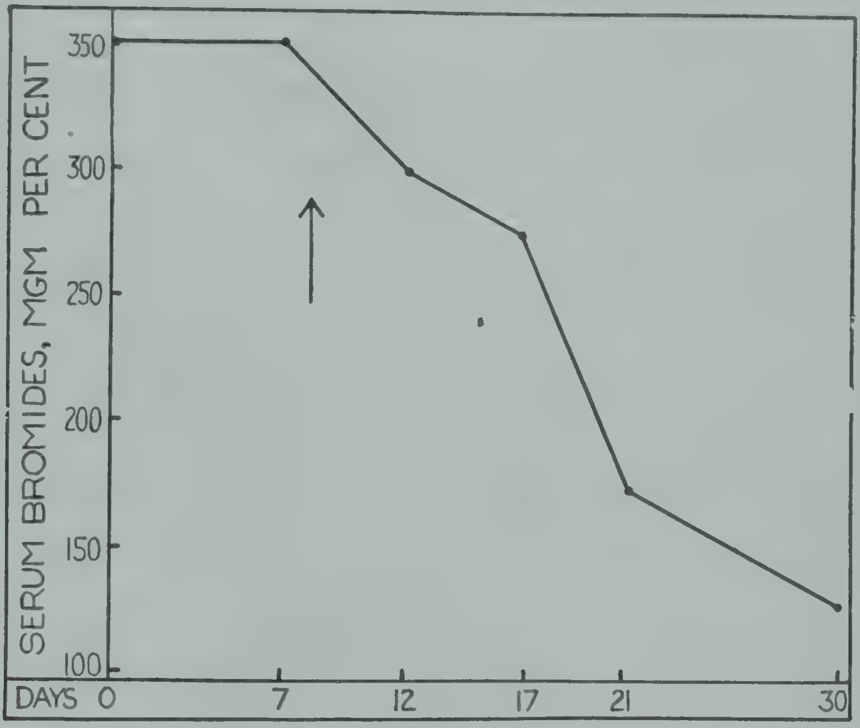


Figure 14. *The effect of the administration of sodium chloride on the rate of elimination of bromide.*

Arteriosclerotic patient, aged 47, with typical symptoms of bromide poisoning. The oral administration of sodium chloride (started at the arrow) hastens the renal excretion of bromides. (After Wagner and Bunbury, 1930. Courtesy of *The Journal of the American Medical Association.*)

In any patient in whom unexplained mental or neurological symptoms exist coincident with a blood bromide value of approximately 75 to 100 mgm per cent (nine to 12.5 mEq), the bromides must be held in high suspicion as the main or contributory cause of the syndrome until they are proved blameless. Withdrawal of bromide and administration of chloride are urgently called for, and the character of the response to treatment will often determine whether bromide was at fault. The urinary content of bromide does not offer a suitable guide in the detection of bromide intoxication.

Treatment of Bromide Intoxication. When the diagnosis of bromide poisoning is made or suspected, all possible sources of bromide ingestion should be investigated and removed. Specific therapy consists in the administration of sodium chloride in order to hasten the elimination of bromide (Figure 14). Sodium chloride is given by mouth, as a rule, but if this is impossible it may be given by hypodermoclysis or intravenous infusion of a sterile 0.9 per cent solution. The dose varies with the severity of the poisoning and the response of the patient, but from six to 12 grams should be given daily in divided amounts in addition to the sodium chloride ordinarily contained in the diet. Some workers experienced in the field believe that if the blood bromide concentration is very high (300 mgm per cent), the administration of extradietary sodium chloride to hasten the excretion of bromide should be delayed until the bromide level has started to fall spontaneously. The reason given is that an exacerbation of bromide intoxication may occur if large amounts of chloride are given. This point is in need of confirmation and adequate explanation.

The fluid intake should be kept at a minimum of 4000 cc per day, in order to correct dehydration if present, to insure diuresis and to prevent loss of body water as a result of the large doses of salt. Adequate intake of food should be assured, by gavage if necessary, in order to combat malnutrition so often associated with chronic bromide intoxication. Enemas and liquid petrolatum may be used to correct constipation. The skin lesions usually clear spontaneously and only the mildest of local measures are indicated. The use of sedatives is usually contraindicated although measures must be taken to combat extreme excitement and delirium. Cold wet sheet packs and continuous tub baths often will allay insomnia and excitement. Recovery requires from one to three or more weeks, when adequate chlorides are administered. When the blood bromide concentration is falling, symptoms of poisoning disappear at a level which is usually higher than that at which they appeared. After recovery, the patient should receive therapy for the underlying condition for which the bromides were originally taken.

Preparations, Doses and Administration. Many different *preparations* of bromide salts are available. These include the bromide salts of sodium, potassium, calcium, strontium, lithium, ammonium, etc. The chief differences in these compounds are their expense and bromide content, but the variation in content of bromide is not sufficiently great to be of practical importance. The official U.S.P. preparations are *Sodium Bromide, Potassium Bromide, Calcium Bromide* and *Ammonium Bromide.* The first two salts are also official in the B.P. Sodium bromide is perhaps preferable, being the least expensive and also the least irritating to the stomach. Ammonium bromide is likely to cause gastro-intestinal distress and is unstable, turning yellow on exposure to air and giving off free bromine. Furthermore, ammonium bromide is an acid-forming salt and may tend to cause acidosis.

A combination of bromides which is rather entrenched in medical tradition is *triple bromides* (*Tablets of Three Bromides,* N.F.; Erlenmeyer mixture), consisting of equal parts of the sodium, potassium and ammonium salts of bromide. It has absolutely no advantages except that it is usually elegantly prepared in effervescent tablets containing citric acid and sodium bicarbonate, which are not unpleasant to take. The N.F. also contains several syrups and elixirs of bromide salts. *Organic bromides* have been exploited for many years by certain drug firms as being less toxic than the inorganic salts. They are expensive and often contain little ionizable bromide. If a bromide preparation is non-toxic, it is also inert therapeutically, because the toxic effects are extensions of the therapeutic effects.

Bromides are always given by mouth, in the form of tablets, capsules, or in solution in syrupy vehicles. The vehicles which especially blind the unpleasant taste are the syrups of citric acid, orange, licorice, cocoa and raspberry, and aromatic syrup of eriodictyon. Medication should be given after meals, and ample water taken with each dose for the dual purpose of lessening gastric irritation and preventing dehydration due to the diuretic "salt action" of bromides.

The *dose of bromides* cannot be stated categorically. It depends chiefly on the end sought and the intake of chloride. Moderate sedation is usually obtained in adults who are in good physical condition from the administration of from three to five grams of sodium bromide daily, provided the patient is eating well. This same amount may prove toxic within a few days to a patient who is dehydrated, eating poorly or not at all, and who has poor renal function. The physician should be alert to the symptoms of bromide intoxication, and medication should not be given, as a rule, for a period of over two to three weeks when patients cannot be kept under surveillance. An exception must be made in the treatment of the epileptic patient whose regimen is well established, whose optimal dose of bromide has been determined, and whose response to therapy over extended periods of time is known. One should prevent the indiscriminate refilling of physicians' orders for bromide by placing the letters (N.R.) on the prescription (page 1310).

Therapeutic Uses. The bromides are valuable as sedatives and for the treatment of epilepsy.

Sedative Uses. Bromides were first introduced for *insomnia* by Behrend in 1864. The somnifacient effects of bromides, however, cannot be expected to ensue from a dose of two or three grams of a bromide salt administered before retiring. Depression of the central nervous system by bromides requires that a sufficiently high concentration of the ion be present in the extracellular fluid, and this is not obtainable from a single therapeutic dose of bromides. The continuous administration of the drug eventually results in sufficient sedative action to overcome sleeplessness, but this action is persistent and disappears only when the bromide level of the blood has fallen sufficiently low. For this reason, when rapid results are necessary, bromides are not the soporifics of choice and one relies on a barbiturate, chloral hydrate or paraldehyde.

For *chronic sedation* of a mild degree, the bromides are probably employed more frequently than any other therapeutic agent. They are serviceable to lessen anxiety and worry, to quiet patients with cardiac disorders or hypertensive vascular disease, to lessen reflex irritability in hyperthyroid states, to control seasickness and the vomiting of pregnancy, to lessen sexual hyperesthesia in nymphomania, satyrism and chordee and after circumcision in adults, etc.

Epilepsy. A special use of bromide is for the control of convulsive seizures in epileptic patients. Bromide salts were the first of the depressant drugs to be employed in epilepsy, and despite the large inroads made by the use of phenobarbital after its introduction in 1912 and more recently by the ketogenic diet and dilantin, bromides continue to be widely used. The anticonvulsant action of bromide depends upon depression of the motor cortex; but the absence of a high selectivity of action as compared to dilantin is apparent in the fact that a certain degree of sedation must be tolerated in order to obtain beneficial effects. Bromides cannot be employed in acute convulsive syndromes, such as strychnine poisoning and tetanus, because of the slow onset of action. The effects of bromide on the cerebral dysrhythmia of epilepsy recordable electro-encephalographically are similar to those of phenobarbital (page 149).

Bromides give only symptomatic relief in epilepsy by reducing both the number and intensity of convulsive attacks. Complete remissions lasting for one or more years occur in approximately 50 per cent or more of all persons with grand mal who are properly treated, but the exact percentage varies from series to series (*see* Pollock, 1938; Stone and Arieff, 1940; Lennox, 1940). Nearly all the remaining patients are benefited in some degree. The data of Lennox on the comparative value of bromide and phenobarbital in relieving seizures and improving the mental status of a large group of noninstitutionalized epileptic patients are given on page 148. Results are most striking when a patient who has had only a few seizures is treated by the use of bromides. The response to treatment is less satisfactory in petit mal; occasionally petit mal may appear after grand mal has been controlled with bromide, and then prove refractory to therapy. Large doses of bromides may make psychic seizures worse or may produce symptoms which resemble the mental or behavioral characteristics of psychic epilepsy. Treatment is less effective in those patients with focal attacks, or if injury or disease of the brain is the cause of the syndrome. In order to maintain an uninterrupted remission, therapy must be continued for years or even throughout life. The opinion held by some authorities that, after several years of freedom from convulsions, a patient may gradually diminish his medication is thought by others to be erroneous.

The dose of bromides for the epileptic patient is that which will keep him free of attacks and yet not cause undue discomfort from the prolonged use of the drug. Adults usually require from 1.0 to 1.3 grams three times daily, this dosage being increased or decreased according to necessity. A diet poor in chloride allows a given dose of bromide to reach more effective concentrations in the blood. The skin should be kept clean to lessen the incidence of bromide rash. Bromide therapy may be combined with phenobarbital medication or used as an adjunct to the ketogenic diet. If one returns to bromide therapy after a period of phenobarbital medication, the latter drug should not be stopped suddenly before the bromide concentration in the blood has been built up to an effective level, or severe seizures and even status epilepticus may result. Epileptic patients on bromide therapy usually carry blood bromide levels of from 75 to 100 mgm per cent, and concentrations of 125 mgm per cent should probably not be exceeded. Obviously, bromide medication is unsatisfactory in patients with status epilepticus or for the acute control of severe and rapidly recurring seizures. The effect of continued administration of bromide on the mentality of epileptic patients is much disputed. Lennox (1940) is of the opinion that persons who are mentally stable (whether epileptic or normal) can take moderate amounts of bromide with impunity, whereas those epileptic persons who are mentally unstable or have psychic variant seizures should better be given other medication. The use of drugs including bromides in the treatment of epilepsy has been reviewed authoritatively by Lennox (1940).

Contraindications. Bromides should not be used for patients with tuberculosis for the same reason that the employment of iodides is usually avoided (page 617). Bromides should also be used with great care, if at all, in patients with advanced arteriosclerosis, debilitation or cachexia, and dehydration. Delirium is readily produced by drugs in individuals with cerebral arteriosclerosis. When diarrhea, vomiting, poor chloride intake, anorexia, etc., are present, the administration of bromides in seemingly safe amounts may rapidly lead to bromide intoxication. In numerous clinical case reports, chronic alcoholism, dehydration and deficient diet played a definite rôle in the development of bromide intoxication. Poor renal function, as in patients with nephritis, also enhances the possibility of poisoning by bromide. Bromide may aggravate the cutaneous lesions of patients with dermatitis, especially acne and dermatitis herpetiformis, or cause an exacerbation of the symptoms of coryza or hay fever.

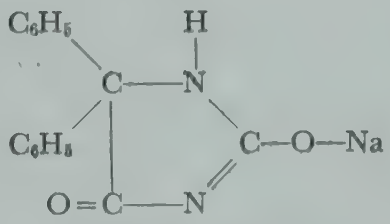
Obviously, no patient with an undiagnosed nervous or mental disturbance should receive the halogen until it is established beyond doubt (*i.e.*, by a blood bromide determination) that his illness is not due to previous bromide ingestion. Bromides should not be prescribed for unlimited periods unless the patient can be kept under close medical observation and an adequate intake of dietary chloride and fluid assured. Proper food and water intake is as important a factor as the exact dose of bromide ingested. Even then, the physician must constantly be on the alert for evidences of beginning intoxication. Bromides should not be prescribed for patients with severe excitement or agitation because the drug is not effective unless dangerously large amounts are given. Delirium due to infectious and toxic syndromes presents an added risk to the safe employment of bromides. Paraldehyde is to be preferred. Bromide has no rational place in the management of patients with depression. Bromides are not analgesic, and their use to allay pain may cause delirium. Inasmuch as bromide medication depresses both libido and potentia, the drug should not be employed when patients with tensional states complain of loss of libido.

The clinical status of bromide therapy has been well summarized by Wagner and Bunbury (1930), as follows: "We do not wish to leave the impression that we consider bromide harmful or even useless as a therapeutic agent. Any one who has had occasion to use bromide realizes that it can be an effective and valuable sedative. We do believe, however, that bromides are used much too indiscriminately and frequently produce harmful rather than beneficial effects. These harmful effects of bromide could be reduced to a minimum if physicians recognized the undesirable mental symptoms of bromide intoxication and were willing to use the simple method described by Wuth for determining the bromide concentration in the blood."

DILANTIN

Historical. Dilantin sodium is sodium diphenyl hydantoinate, a drug closely related to nirvanol. In an extensive experimental study of anticonvulsants by Merritt and Putnam (1938), dilantin sodium was found to possess the greatest anticonvulsant activity combined with the least hypnotic effect of the many drugs investigated. The experiments were conducted on cats and convulsions were produced by controlled and quantitated electrical stimuli (Putnam and Merritt, 1937). Dilantin sodium was found to be as anticonvulsant as phenobarbital but to lack the depressant effects of the latter drug. After preliminary toxicity studies on animals had been performed, Merritt and Putnam (1938) introduced dilantin sodium as an agent to control convulsive seizures in epileptic patients. The Council accepted dilantin sodium for inclusion in N.N.R. (*see* the Report of the Council, 1939).

Chemistry and Preparations. *Dilantin Sodium,* N.N.R., is the proprietary name for *sodium diphenyl hydantoinate,* the structural formula for which is as follows:



Dilantin Sodium

The close chemical relationship of dilantin to nirvanol is at once apparent, an ethyl group in the latter being replaced by a phenyl radical. This relationship accounts for the toxic side-actions noted with dilantin, many of which resemble those occurring with the use of nirvanol. Dilantin is also closely allied to the barbiturates, being a derivative of glycolyl urea instead of malonyl urea.

Dilantin sodium is a white, odorless, microcrystalline powder with a slightly bitter taste. It is marketed for oral administration in sealed capsules, each containing 0.1 or 0.3 gram of drug. Aqueous solutions are alkaline, and the drug is completely soluble in water only when the solution is adjusted to pH 11.7, thus making parenteral adminstration impracticable. The chemical is soluble in alcohol.

Pharmacological Actions. The pharmacological and toxicological effects of dilantin in animals have been reported by several investigators (*see* Gruber and coworkers, 1940; Haury and Drake, 1940). Toxic doses produce death by respiratory failure or asphyxia from convulsions, and elicit nystagmus, mydriasis, panting, hyperpyrexia, spastic gait, tremors of the neck muscles, salivation and vomiting, peripheral vasodilatation and fall in blood pressure, defecation with liquid stools, urination, and opisthotonic convulsions.

Doses in the therapeutic range have been shown to be innocuous for a large variety of laboratory animals and long-continued medication with such amounts are without apparent ill effect. Cats, dogs, rabbits and rats withstand massive single doses of dilantin administered orally. For example, the minimal lethal dose of dilantin by mouth for the rat is 1.6 grams per kg; for the rabbit, 3.4 grams per kg. Dilantin is considerably more toxic when administered intravenously or intraperitoneally.

The mechanism by which dilantin prevents electrically induced convulsions in animals and epileptic seizures in man is unknown. That the action is highly selective for the motor cortex is indicated by the fact that the drug apparently does not depress other functions of the brain. The threshold of corticomotor excitability in animals is raised two- to four-fold, whereas a dose of sodium bromide sufficient to prevent a cat from walking causes only a 50 per cent increase in the threshold. Similarly, an amount of phenobarbital causing an equivalent increase in the threshold to that of dilantin produces marked hypnotic effects (Merritt and Putnam, 1938) (Figure 15).

The data concerning the action of dilantin on convulsions experimentally induced in human beings is as yet meager. Frost (1939) found that the drug did not lower the convulsive threshold dose of metrazol administered intravenously in three insane patients. However, Goldstein and Weinberg (1940), employing a larger series of patients, concluded that dilantin diminished the frequency of convulsive phenomena induced in epileptic subjects by the subcutaneous injection of metrazol, particularly in those individuals with grand mal.

That dilantin may exert other effects than that on cortical excitability, however, is suggested by the facts that psychomotor equivalent attacks are relieved and that many epileptic patients become better behaved and more amenable to discipline after administration of the drug (Merritt and Putnam, 1938, 1940). The action of dilantin on the characteristic cerebral dysrhythmia underlying epilepsy is not fully known at present. Whereas phenobarbital and bromides prevent or abort the electrically recordable dysrhythmia of petit mal (page 149), dilantin may not necessarily improve the electroencephalogram of epileptic individuals who are, nevertheless, rendered free of seizures. On the other hand, the electrical record of patients who are abruptly and completely relieved of attacks, especially of the psychomotor variety, may become essentially normal (unpublished data of Merritt and Lennox, cited by Lennox, 1940). Apparently it is possible to relieve major seizures without improving the cerebral dysrhythmia.

Absorption, Fate and Excretion. Dilantin is satisfactorily absorbed from the intestinal tract. Only 2.5 to 10 per cent of the orally administered drug is recoverable in the feces and less than 0.1 per cent is found in the urine. The fate and distribution of dilantin in the tissues are unknown, but the drug apparently disappears from the body fairly promptly. Evidently several days are required to build up an effective level of dilantin in the brain because if phenobarbital is prematurely withdrawn when dilantin is started, epileptic attacks may become more frequent.

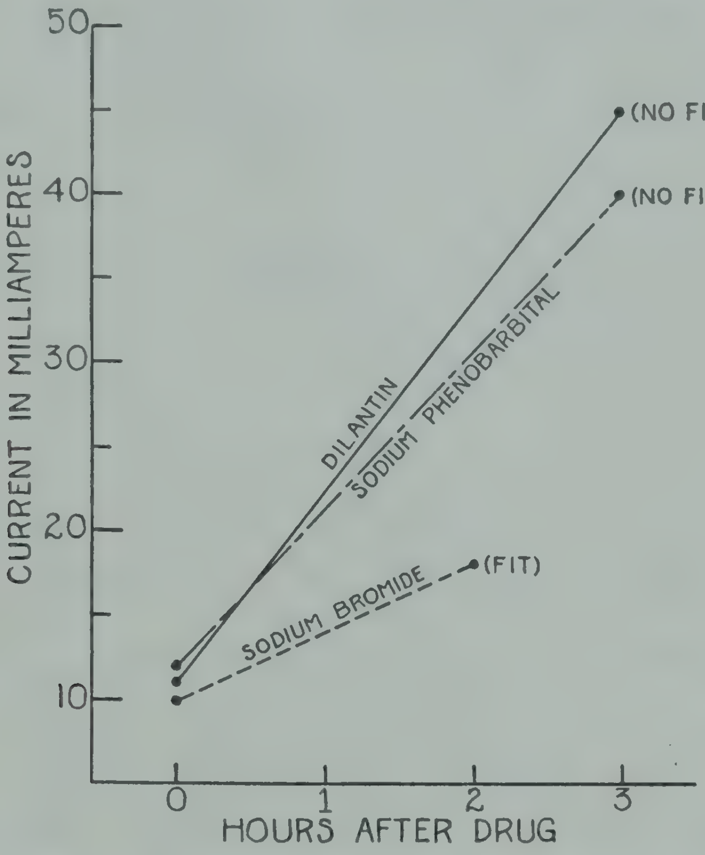


FIGURE 15. *The effect of anticonvulsant drugs on electrically-induced convulsions in cats.*

Dilantin, in doses producing minimal depression of spontaneous activity, increased the convulsive threshold to such an extent that a fit could not be produced with maximal currents. *Phenobarbital* exerted a similar anticonvulsant action only in doses which produced definite central depression. *Sodium bromide* was a poor anticonvulsant and, in doses causing marked depression, did not significantly increase the convulsive threshold. (After Merritt and Putnam, 1938. Courtesy of the *Archives of Neurology and Psychiatry.*)

Dosage. The initial dose of dilantin sodium for adults is 0.1 gram two or three times daily. This dose may be gradually increased if necessary until the optimal amount is reached. This optimal dose level must be determined by trial and error for each patient, and varies between 0.2 and 0.6 gram daily. The majority of adults tolerate 0.3 to 0.4 gram daily without toxic effects. Rarely does a patient tolerate a total daily dose larger than 0.6 gram. So critical is the effective anticonvulsant level of the drug that a reduction of the optimal dosage by 0.1 gram daily may result in the recurrence of attacks.

Children over six years of age may be started on a dose of 0.1 gram two or three times daily for one week, and this amount may then be increased to 0.4 gram daily if necessary. Small children (under four years of age) may be given 0.03 gram twice daily, the drug being mixed with cream to disguise the bitter taste and to lessen gastric irritation. If necessary, the number of doses may be increased cautiously to three or four per day.

If bromide or phenobarbital is being employed and it is desired to substitute dilantin, the former drugs should be discontinued gradually over a period of four to seven days while dilantin is being substituted. Otherwise, an increase in the number and severity of attacks may occur.

In some cases, dilantin can be administered in larger doses to coincide with the periods when seizures are likely to be most frequent. For example, nocturnal attacks may better be prevented by giving a greater portion of the total dose before bedtime, and women whose seizures occur especially at the time of the menstrual period may be given additional doses on the critical days. Adequate treatment must still be given in the interim.

Dilantin should be taken with at least half a glass of water with meals or just after meals in order to lessen the gastric distress frequently caused by the alkalinity of the drug. In occasional patients, nausea and vomiting may be severe. Relief may sometimes be obtained by giving one cc of dilute hydrochloric acid with each dose of dilantin.

Therapeutic Uses. The only known clinical use of dilantin at present is in the treatment of epilepsy, or in the diagnosis of so-called "epileptic-equivalents." Many reports have appeared testifying to the value of dilantin in epilepsy (*see* the review of Lennox [1940] on the drug therapy of epilepsy), but only those publications recording large series of cases can be analyzed here. Merritt and Putnam (1938) originally reported the following results: In 118 patients with grand mal, complete relief was obtained in 58 per cent and a marked reduction in the number of attacks occurred in 27 per cent. In 15 per cent, only a moderate degree of benefit or no improvement over the previous therapy with bromides or phenobarbital was noted. In 74 patients with petit mal, complete relief was obtained in 35 per cent, a marked reduction in the number of attacks in 49 per cent, and slight or no improvement over the prior status in 16 per cent. In six patients with psychomotor equivalent attacks, four were completely and two moderately relieved by dilantin. Subsequent reports by Merritt and Putnam (1939, 1940) on larger series of patients indicate the same general results. The drug appeared most effective in relieving psychic equivalent attacks, 12 of 19 patients experiencing complete relief. Of 20 other patients with psychic equivalents associated with grand mal, 12 were completely relieved. This is particularly stressed because of the inadequacy of bromides and phenobarbital in the management of this form of epilepsy. The over-all efficacy of dilantin in the 350 patients studied by Merritt and Putnam, most of whom had not been relieved by other drugs, surgical procedures or the ketogenic diet, may be appreciated from the fact that 79 per cent found dilantin more effective than any form of previous therapy.

In 129 epileptic children in whom Kimball (1939) used dilantin for more than three months, seizures were entirely controlled in 81 (62.7 per cent), definitely alleviated in 19 (14.7 per cent) and little or not at all benefited in 29 (22.5 per cent), a finding in substantial agreement with that of Merritt and Putnam. Kimball also reported that the mental state, memory, ability to concentrate, emotional stability and personality of his patients were greatly improved in comparison with the condition noted while on other therapy. In a later publication, Kimball and Horan (1939) reported their results with dilantin sodium therapy in a series of 220 children and young adults, most of whom had been using the drug for six months or longer and 50 of whom had been on dilantin for over a year. Seizures were entirely controlled in 55 per cent and partially controlled or modified in 20 per cent of the cases. In 25 per cent, there was little or no improvement.

Numerous other investigators have reported on the anticonvulsant properties of dilantin. These include Williams (1939), Blair and associates (1939), Frankel (1940), Butter (1940), Coope and Burrows (1940), Robinson and Osgood (1940), Fetterman (1940), and many others. The Report of the Council (1939) summarizes the results obtained in 595 patients treated by thirteen physicians and indicates that there is an unanimity of opinion regarding the fact that epilepsy is definitely improved as far as major seizures and psychic equivalent attacks are concerned. Of the 595 cases, dilantin was reported to be the most effective form of therapy in 404.

The combination of dilantin and phenobarbital appears to be especially beneficial in a number of patients in whom neither drug alone allows satisfactory relief of symptoms. The potentiation of effects obtained by this combination is often quite dramatic (Cohen and coworkers, 1940; Robinson and Osgood, 1940; Ebaugh, 1940). Petit mal may also be managed more satisfactorily by using both drugs together (Cobb, 1939). Promising results with dilantin in the treatment of epilepsy in psychotic patients likewise have been reported (Frost, 1939; Black, 1939).

Clinical Toxicity. Toxic reactions from dilantin occur in approximately 15 per cent of patients. These are usually mild, do not interfere with therapy and may often be relieved by proper adjustment of the dosage. Untoward effects are referable mainly to the central nervous system, gastro-intestinal tract, skin, and gums.

Central Nervous System. Reactions referable to the central nervous system include giddiness, ataxia, nervousness, tremors, nystagmus, head-nodding, diplopia, blurring of vision, ptosis, ocular pain, and slurring of speech. In some patients the drug may cause fatigue, apathy or confusion, drowsiness, and headache. In others insomnia, irritability, and quarrelsomeness may be noted. Rarely delusions, hallucinations and other psychotic manifestations may appear. In addition, there may be experienced difficulty in breathing and swallowing. These phenomena tend to appear between the third and tenth day of treatment and reduction in dosage usually brings prompt relief. If seizures are not held in abeyance by the smaller amounts of the drug, the dose of dilantin may be increased after a few days without necessarily initiating a recurrence of toxic effects. Untoward responses are more frequently observed if the dose level employed is above 0.5 gram daily.

Gastro-intestinal Tract. The gastric distress caused by the alkalinity of dilantin can usually be averted by taking the drug after meals or with dilute hydrochloric acid, as already stated. *Acute gastric upsets,* suggestive of chronic irritation, have also been reported (Kimball and Horan, 1939). The clinical picture is suggestive of the acute abdomen and is characterized by considerable epigastric pain and soreness, severe nausea and vomiting, and complete anorexia. Fever, leukocytosis and abdominal rigidity, however, are absent. The attack may last 48 hours and some patients have been operated upon for appendicitis. Apparently the gastric disturbance occurs only in those who have taken dilantin sodium for a long period of time and who have developed hyperplastic gums. Gastroscopic studies of one case revealed a recent submucosal hemorrhage and a second patient had a fatal hematemesis. In all, 62 gastro-intestinal attacks were observed in the series reported by Kimball and Horan.

Skin. Dermatitis is rather frequent after dilantin, occurring in five per cent of the 350 patients reported by Merritt and Putnam (1939), but the condition is rarely serious. The incidence of morbilliform rash in the 220 patients reported by Kimball and Horan (1939) was 10 per cent. The cutaneous eruptions due to dilantin may be erythematous, scarlatiniform or morbilliform in character, usually appear about the tenth day (seventh to fifteenth) of treatment, are often accompanied by fever, leukocytosis and occasionally by bronchial irritation, and are most often seen in children and young adults. The syndrome is reminiscent of the drug fever noted after sulfanilamide and resembles in many respects that caused by nirvanol. The rash disappears in all patients, however, regardless of whether dilantin is continued. Serious forms of dermatitis are evidently quite rare. Merritt and Putnam (1938) reported an instance of exfoliative dermatitis appearing 40 days after therapy was started and disappearing rapidly upon immediate discontinuance of the drug. They also recorded one patient in whom there occurred purpuric lesions confined to the buttocks and unaccompanied by constitutional symptoms or hematological abnormalities. The lesions cleared uneventfully, despite continuance of dilantin.

Hyperplasia of the Gums. An interesting and peculiar reaction which has been noted accompanying dilantin therapy is the development of *hyperplasia of the gums.* This occurs almost exclusively in children or young adults. The incidence of the reaction evidently varies considerably in different series. Hyperplasia of the gums was noted in 68 of 119 epileptic children receiving dilantin and examined by Kimball (1939), in 112 of the 220 patients reported by Kimball and Horan (1939), and in 30 of the 48 cases reported by Frankel (1940). The degree of gingival hyperplasia varies considerably and could be considered advanced in approximately one-quarter of individuals showing the reaction. The tissue change may appear within the first few months of therapy in some individuals, whereas in others it may not develop despite prolonged medication with dilantin. The incidence of gingival hyperplasia reported by Merritt and Putnam (1939) is considerably lower than those already cited. Only six per cent of their 350 patients receiving dilantin for periods up to two years developed the tissue change.

Soreness of the mouth and tender gums may appear from two to four weeks after starting dilantin and may precede the hyperplasia of the gums. Occasionally sponginess, bleeding on pressure and gingivitis may accompany the tissue overgrowth, but these features are mild or absent if oral hygiene is good. The condition does not cause the patient inconvenience, and dilantin need not be discontinued. Biopsy of the hypertrophic gum tissue in two patients (Kimball and Horan) showed a marked proliferation of the mucous membrane and connective tissue, suggesting chronic irritation.

The suggestion has been made that the hyperplasia is related to low vitamin C levels in the blood, but there is little evidence to substantiate the belief that the anomaly is in any way associated with scurvy or abnormal vitamin C metabolism. Indeed, experiments on animals do not indicate that dilantin influences the utilization of ascorbic acid (Report of the Council, 1939); and Gruhzit (1939) has shown that a vitamin C deficiency is not produced by the drug.

Miscellaneous Reactions. Hirsutism, especially in adolescent girls, has been reported to occur in rare instances. Swelling of the face has also been noted. The blood of some patients on dilantin therapy may show a slight leukocytosis and occasionally a mild eosinophilia.

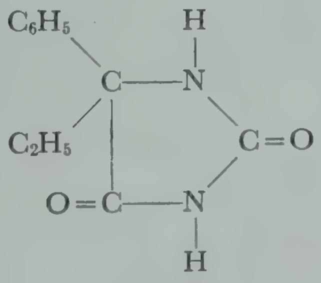
Status. Treatment with dilantin appears to be at least as effective in epilepsy as therapy with bromide, phenobarbital, or the ketogenic diet. That dilantin may prove superior to these measures is indicated by the fact that many of the patients reported to respond favorably to dilantin therapy had failed to respond to other measures. A distinct advantage of dilantin therapy is that the sedative effect of bromides and phenobarbital is avoided. Also noteworthy is the striking improvement in patients with seizures of the psychomotor (psychic equivalent) type, a form of epilepsy which is not often improved and which might even be aggravated by bromides or phenobarbital. Least promising results are obtained with dilantin in cases of petit mal in which there is transient loss of consciousness without muscle movement, and most promising results are recorded in grand mal in which dilantin is probably superior to phenobarbital. The drug may also be employed as a diagnostic test in questionable cases of so-called "epileptic equivalent." Finally, the mentality of many patients becomes clearer, either as a result of fewer seizures, or due to an effect of dilantin on the basic cerebral dysrhythmia characterizing epilepsy.

More work and experience are required to determine the toxic potentialities of dilantin, especially in regard to the cause and significance of the gingival hyperplasia and gastric episodes. At present, however, many thousands of patients have been treated continuously with the drug for periods ranging from several months to over three years with only occasional serious mishap, and scores of favorable clinical reports have been published. This in itself does not offer assurance that chronic medication with dilantin is innocuous and therefore patients receiving the chemical should be kept under close medical surveillance and impressed with the necessity of continuing under observation.

Dilantin must be placed in the same category as nirvanol, the toxic properties of which have long been known. Although dilantin has a greater margin of safety in respect to the fatal dose than bromides or phenobarbital, it causes more toxic reactions of a mild degree when used therapeutically. For the present it may be safest to restrict the administration of dilantin to those epileptic patients who fail to respond satisfactorily to better known methods of therapy (Council Report, 1939). The appearance of purpura or serious dermatitis should call for immediate discontinuance of dilantin, and an exfoliating eruption demands that the drug be withdrawn permanently. If drug rash or drug fever occurs in a mild form, dilantin may be cautiously resumed after a rest period. Certainly all the contraindications to dilantin are not yet known. Nor has it been determined whether patients become refractory to the drug after a long period of satisfactory response.

NIRVANOL

Nirvanol (phenyl-ethyl-hydantoin) is chemically allied to the barbiturates and was introduced into medicine as a sedative and soporific. Its chemical structure is as follows:



Nirvanol

Interest in nirvanol lies in the fact that at one time it enjoyed some favor in the therapy of *chorea* in children, and that it is closely related to dilantin, a drug of value in epilepsy. The use of nirvanol in chorea was discovered by accident when it was noted that the drug, given for sedation, arrested choreiform movements. It is now known that the action is not specific and depends upon toxic effects. Although nirvanol is still used, it has never gained much favor in the United States.

Nirvanol produces what has been termed the "nirvanol reaction" or "nirvanol sickness." Within one to two weeks after the oral administration of daily doses of 0.3 gram, a morbilliform rash and fever appear. The maculopapular eruption spreads from the trunk to the limbs and disappears in from four to five days. The temperature may reach 104 F. or higher. Few other symptoms are noted in most cases except that some children develop cervical adenitis, conjunctivitis and pharyngitis. The changes in the blood are quite interesting. Eosinophilia is the most striking and constant feature. There also occurs a leukopenia with a relative lymphocytosis and monocytosis. Occasionally, agranulocytic changes have been observed.

In the treatment of chorea, nirvanol is given with the object of producing the typical pyrexial, hematological and cutaneous reactions, because otherwise beneficial results are not observed. The maximal dose is 0.3 gram daily in divided doses for not over two weeks, and medication should cease as soon as rash or fever develops. It is claimed that the more marked the reaction, the greater is the improvement. It is interesting that, should a subsequent course of the drug be given, the temperature rise and rash are not noted, but only eosinophilia appears. A third course may not even elicit eosinophilia.

Status. Nirvanol is not an official drug and is not included in N.N.R. It should not be employed either as a sedative or for chorea. The benefit noted in some cases of chorea apparently depends on the fever, and safer methods of fever therapy are available for choreic children. The disease is characterized by marked fluctuations in its severity and by spontaneous remissions. It would thus be unwise to conclude either that nirvanol is a specific or that it has benefited all the cases which improve while under treatment with it. Similar remission has been noted after a toxic reaction of fever and rash secondary to the administration of phenobarbital for sedation. Finally, nirvanol is dangerous in that it may cause severe skin reactions of an exfoliative type, accompanied by cyanotic swelling of the eyelids and face, and inflammation of the tonsils, pharynx, gums and conjunctiva. The liver and kidneys are also occasionally involved, and bronchopneumonia and agranulocytosis may occur.

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CHAPTER 11

HYPNOTICS AND SEDATIVES

III. CHLORAL HYDRATE, PARALDEHYDE AND MISCELLANEOUS AGENTS

CHLORAL HYDRATE

Historical. Chloral hydrate, first made by Liebig in 1832, was introduced into medicine by Liebrich in 1869, at a time when cannabis, alcohol and morphine were the main central depressants. Liebrich wrongly believed that chloral hydrate would be changed to chloroform in the body and in this manner exert its hypnotic action. Chloral hydrate is the oldest member of the hypnotic group, and clinical studies show that it is still one of the cheapest and best.

Chemistry. Chloral hydrate is a chlorinated derivative of ethyl alcohol. There is an entire series of chlorals, but the one of greatest medicinal value is chloral hydrate. When chlorine acts as an oxidizing agent on alcohol, chloral (CCl_3CHO), an oily liquid, is formed. Hydration of *chloral* yields *chloral hydrate,* $CCl_3 \cdot CH(OH)_2$, a crystalline substance.

Pharmacological Actions

Local. Chloral hydrate is quite irritating to the empty stomach and therefore must be given well diluted or it will cause nausea and vomiting. The irritating property of the drug is the basis for its use in rubefacient liniments, such as *Camphorated Chloral,* N.F., which is a liquid containing equal parts of camphor and chloral hydrate. Cutaneous erythema, warmth and slight local anesthesia result from its surface application; but, if larger amounts or longer contact are employed, pain, vesiculation and necrosis of the skin occur. Chloral hydrate is also used in conjunction with phenyl salicylate in the prophylaxis of epidermophytosis of the feet, and with salicylic acid in the treatment of warts.

Systemic Actions. Chloral hydrate has the typical action of the methane series of anesthetics. It is never used for general anesthesia, however, because the margin of safety is too narrow with the large doses required for this purpose. The main use of chloral hydrate is as a sedative and soporific. Its analgesic powers are weak, as is the case with all the hypnotics.

In ordinary doses of one or two grams, chloral hydrate causes sedation, ordinarily without preliminary excitement, in from 10 to 15 minutes. Sleep occurs within the hour. It is a quiet and deep sleep, often accompanied by dreams, and lasts from five to eight hours; but sleep is not so deep that the patient cannot be readily aroused. For all these reasons, it has been called "physiological sleep."

Generally there are no after-effects and no "hangover." Reflexes are not greatly depressed and therefore chloral hydrate is not the best anticonvulsant. Rarely, therapeutic doses of chloral hydrate may cause excitement or delirium, especially in the presence of pain, and the patient may appear to be inebriated.

Doses somewhat larger than the therapeutic cause deeper and longer sleep and also obtund pain. With very large doses, six grams or over, it is possible to obtain complete anesthesia, but this is dangerous because such amounts approach too closely those capable of causing respiratory paralysis.

Blood Pressure and Respiration. These functions are little more depressed by chloral hydrate than by ordinary sleep. The blood pressure may fall slightly from muscular inactivity and peripheral vasodilatation as a result of mild central vasomotor depression. The respirations are somewhat slower than in normal sleep.

Heart. The belief that chloral hydrate depresses the heart is largely erroneous. While it is true that the drug may cause cardiac depression, as can many of the halogenated hydrocarbons, there is no good clinical evidence of any deleterious effect on the heart from the continued use of therapeutic doses (Alstead, 1936). Untoward cardiac effects occur only with toxic doses in patients with heart disease.

Absorption, Fate and Excretion. Chloral hydrate is absorbed readily from the gastro-intestinal tract. It has long been believed that chloral hydrate is reduced in the body to trichlorethylalcohol, CCl_3CH_2OH, in itself a potent hypnotic. This alcohol is then combined, principally in the liver, with glycuronic acid to form trichlorethylglycuronic (urochloralic) acid which is not hypnotic. Detoxification of chloral hydrate occurs over a period lasting several hours.

The fate of chloral hydrate has been called into question by Lehman and Knoefel (1938) who found that trichlorethylalcohol is more powerfully hypnotic than chloral hydrate and that the latter's potency and duration of action cannot easily be explained on the basis of reduction of the hydrated aldehyde to the alcohol. Furthermore, when chloral hydrate is given, little urochloralic acid is recovered from the urine, whereas more appears after trichlorethylalcohol.

The pharmacological actions of *trichlorethylalcohol* ($CCl_3 \cdot CH_2OH$) have been studied in comparison with tribromethanol by Lehman and Knoefel (1939), and the results of animal experiments suggest that the drug may prove of clinical value as a basal anesthetic.

The urine of patients receiving full doses of chloral hydrate may give a false positive test for sugar. The elimination of chloral hydrate in the urine has been proposed as a test for liver function (Mukerji and Ghose, 1939).

Poisoning. *Acute.* The toxic dose of chloral hydrate for adults is approximately 10 grams, although death has been reported to occur from as little as four grams. On the other hand, a single dose of 30 grams was not fatal to one patient, nor was 20 grams given daily for three days to another. Nevertheless, care should be exercised in giving more than two grams of the drug as a single dose. The usual features of poisoning by chloral hydrate are deep stupor, marked vasodilatation, low blood pressure, fall in body temperature, slow respiration and cyanosis. Gastric irritation may result in initial vomiting. Occasionally delirium occurs, or prompt collapse. Pin-point pupils may be seen, as with morphine poisoning. Icterus due to liver damage and albuminuria from renal irritation may appear if the patient survives. Death results from respiratory depression, usually within five to 10 hours. In patients with impaired hearts, cardiac collapse may cause death.

Acute poisoning may also occur from the combination of liquid chloral and alcohol, so-called "knock-out drops" ("Mickey Finn"). Apparently, such a mixture is quite potent and rapidly depressant. It was long believed that chloral alcoholate was formed by the combination of alcohol and chloral and that this compound accounted for the enhanced depressant properties of the mixture. However, Adams (1940) was unable to find any data in support of the belief that chloral alcoholate is more toxic than chloral hydrate, and his experiments in rats even indicate that the alcoholate is slightly less hypnotic and less toxic than the hydrate.

Treatment of acute poisoning consists in gastric lavage, warmth, stimulants for the respiration and blood pressure, artificial respiration if needed, and in general the same measures employed in barbiturate poisoning. In addition, hypertonic glucose solution should be given intravenously not only to combat shock, maintain blood pressure and promote diuresis but also to protect the liver against damage.

Chronic Poisoning. This occurs especially in persons with the "*chloral habit,*" common formerly but rare today. The continued use of chloral hydrate leads to habituation and a slight degree of tolerance. Chloral hydrate habitués often rapidly develop an impaired mechanism for the detoxification of the drug and sudden death may occur from what formerly was termed a "break in tolerance," which is due either to an overdose or to the failure of the detoxification mechanism as a result of liver damage. Parenchymatous renal injury may also occur. The chloral habitué bears many clinical resemblances to the chronic alcoholic addict, but usually has a more severe gastritis. Skin manifestations are sometmes seen and may be erythematous, urticarial or even purpuric.

Treatment consists of withdrawal of the drug, correcting the basic cause of the habituation, and rehabilitating the patient. It is essentially similar to that for alcoholic addiction. Sudden withdrawal may occasionally produce a clinical picture similar to delirium tremens.

Preparations and Doses. *Chloral Hydrate,* U.S.P., B.P., is a colorless, transparent crystalline substance with an aromatic, penetrating, acrid odor and a slightly bitter, pungent taste. It is very soluble in water, alcohol and oils and can therefore be dispensed in a number of ways, but it has many incompatibilities. The drug forms a liquid when mixed with many substances, especially camphor and menthol. It should not be given in any strongly *alcoholic* vehicle because chloral alcoholate may be formed. The N.F. contains a preparation consisting of chloral hydrate (25 per cent), potassium bromide (25 per cent) and extracts of hyoscyamus and cannabis in distilled water, known as *Elixir of Bromide and Chloral.*

The usual adult hypnotic dose of chloral hydrate is 0.5 to 1.0 gram, but two grams may be given if necessary. Larger amounts are used in cases of mania or delirium, but these should be given with care. In prescribing chloral hydrate for oral use, one should guard against gastric irritation. The drug is too hygroscopic to be prescribed in capsules and must be given in solution. The syrups of orange and citric acid mask the taste fairly well, and solutions of the drug in such vehicles should be taken well diluted with water or milk. Chloral hydrate is too irritant to be given hypodermically, but can be given rectally in solution in olive oil or some other bland fixed oil.

Uses. The *sedative and soporific uses* of chloral hydrate are similar to those of the barbiturates and paraldehyde. The poor analgesic properties of the drug do not permit its effective use alone in the presence of pain. Chloral hydrate is frequently used in patients undergoing morphine or alcohol withdrawal, and in delirium tremens. At one time, it was also considered particularly valuable in the management of eclampsia (Stroganoff treatment) for which purpose chloral hydrate was administered rectally at intervals. If convulsions are actually present, the barbiturates given intravenously are to be preferred.

Chloral hydrate is *contraindicated* in patients with marked hepatic or renal impairment and severe cardiac disease. If gastritis is present, the drug should not be given orally but may be administered in olive oil as a retention enema.

Chloral hydrate is unfortunately neglected today. The ease with which the barbiturates are dispensed and the prominence given them in medical literature and in advertising have caused the physician to lose sight of the fact that chloral hydrate is still one of the cheapest and most effective hypnotics (Grabfield, 1931, 1936).

OTHER CHLORAL HYNOPTICS

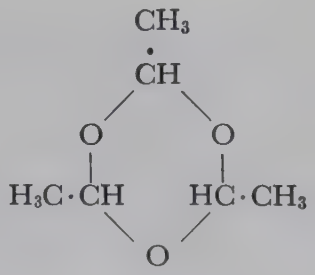
Butylchloral Hydrate, N.N.R., $CH_3CHCl \cdot CCl_2CH(OH)_2$, is a crystalline white powder with a pungent odor and acrid taste and soluble 1:50 in water and 1:1 in alcohol. It has much the same hypnotic properties as chloral hydrate and is said to possess some analgesic value in addition. The adult dose is 0.3 to 1.0 gram and the drug may be given orally in capsules.

Chlorobutanol (*Chlorbutol*), U.S.P., B.P., $Cl_3C.C(CH_3)_2.OH$, has the advantage over chloral hydrate of not causing gastric irritation. In fact, it has a local anesthetic action and may be used as an anesthetic dusting powder (one to five per cent) or ointment (10 per cent), or may be taken orally to allay vomiting due to gastritis. The drug consists of colorless crystals with a somewhat camphoraceous odor and taste and is soluble in water 1:125 and in alcohol 1:1. The hypnotic oral dose for adults is 0.3 to 1.0 gram, given as tablets or in capsules. The drug is also serviceable as a preservative in solutions of epinephrine, posterior pituitary, etc.

PARALDEHYDE

Historical. Paraldehyde was introduced into medicine by Cervello in 1882. It is still considered a very efficient hypnotic, but is not used as frequently as it deserves to be.

Chemistry. Paraldehyde (paracetaldehyde) is a polymer of acetaldehyde, in which three molecules of the latter are joined in a cyclic structure. The suggested formula is as follows:



Paraldehyde

Paraldehyde is a colorless transparent liquid which has a strong, characteristic pungent odor and a burning, disagreeable taste. It is soluble in water only to the extent of one part in eight, but is freely miscible with alcohol and oils. Paraldehyde remains sterile and requires no preliminary treatment before parenteral use. It is easily inflammable.

Pharmacological Actions. The action of paraldehyde on the central nervous system is similar to that of chloral hydrate. With the ordinary hypnotic dose of four to eight cc, sleep ensues in 10 to 15 minutes, more promptly than with any other sedative. Therefore, the patient should be in bed and prepared to retire when the drug is taken. The sleep produced is quite normal and without after-effects. Paraldehyde rarely causes preliminary symptoms of excitement. The soporific effects are not as potent or certain as those of chloral hydrate, but therapeutic or even larger doses do not depress the respiration or circulation. Paraldehyde is not analgesic, although large doses cause sleep despite the presence of pain.

Absorption and Excretion. Paraldehyde is absorbed rapidly from the gastrointestinal tract, and also from intramuscular sites of injection. The characteristic odor of paraldehyde, similar to that of fusel oil, appears on the breath within a few minutes after ingestion of the drug. The fate of paraldehyde in the body is unknown. In dogs, it apparently is oxidized in large part (Defandorf, 1939). The experiments of Levine, Gilbert and Bodansky (1939) suggest that the liver is an important seat for the destruction of paraldehyde. Following liver injury induced in dogs by chloroform, administration of paraldehyde resulted in prolonged hypnotic effects and elevated blood paraldehyde curves, indicating decreased ability of the liver to detoxify the compound. That fraction of the ingested paraldehyde which escapes destruction in the tissues is excreted unchanged largely by the lungs, and in smaller part by the kidneys. In some species (rat), paraldehyde is quantitatively excreted by the lungs. Paraldehyde is not contraindicated in patients with renal disease as is chloral hydrate for which the kidney is an obligatory channel of excretion.

Toxicity. The acute toxicity of paraldehyde is low, and the drug possesses a wide margin of safety. Very large doses cause only prolonged unconsciousness, fatalities being quite rare (Kotz, Roth and Ryon, 1938). As much as 104 cc has been taken in a single dose; the patient recovered after a 32-hour sleep; 120 cc were mistakenly given rectally to a woman in labor without fatality (Hanson, 1937). On the other hand, a dose of 31 cc given rectally has caused death. Impaired hepatic function may play a rôle in the occasional case of hypersusceptibility to paraldehyde. The symptoms and treatment of acute poisoning are the same as those for chloral hydrate. The diagnosis is facilitated by the characteristic odor of the breath.

Tolerance and Habituation. Some degree of tolerance to paraldehyde may occur with its continued use. Habituation develops rather infrequently, due mainly to the fairly disagreeable odor and taste of the drug. The paraldehyde habitué resembles the alcoholic addict, may even experience delirium tremens, and is treated in the same manner.

Preparations and Dose. *Paraldehyde,* U.S.P., B.P., is usually given orally in doses of three to eight cc. One may increase this to 10 or 15 cc if necessary. The drug is difficult to dispense, due to its poor solubility in water and unpleasant taste. Syrups of orange and cinnamon may serve as vehicles, or paraldehyde may be taken in milk, fruit juices or wine. It can also be given in iced water or tea, or on cracked ice. Paraldehyde can be dispensed in gelatin capsules, but this, as a rule, is too troublesome and expensive. A convenient way, especially if the patient cannot cooperate or needs large doses, is to administer the drug rectally as a small retention enema. For this purpose, 10 to 20 cc may be mixed with one or two parts of olive oil in order to avoid the discomfort of rectal irritation, or one cc of benzyl alcohol may be added to the paraldehyde for the same purpose.

Status. Paraldehyde is one of the best and least toxic hypnotics. Despite the odor and the difficulty of dispensing it in a pleasant form, paraldehyde deserves a wider popularity than it enjoys at present. Many physicians feel that ease of administration of hypnotic drugs, as is the case with the barbiturates, encourages their misuse.

Uses. The indications for the soporific use of paraldehyde are the same as for other hypnotic agents. Due to its odor, paraldehyde cannot often be employed for the purpose of mild sedation in ambulatory cases. In delirium tremens, paraldehyde is often administered to quiet the patient and produce sleep, for which very large doses (15 to 30 cc or more) are needed.

Paraldehyde may be used in emergency for strychnine or cocaine convulsions, if a soluble barbiturate is not available. It is given slowly intravenously, usually diluted with several volumes of sterile physiological sodium chloride solution. When paraldehyde is given intravenously, central depression may be preceded by a few seconds of excitement or coughing. The intravenous route is not without danger, for the drug may very occasionally cause circulatory collapse or pulmonary edema, and should be injected only if absolutely necessary. The dose by vein is four or five cc, but the injection should be stopped as soon as the desired degree of depression is obtained. Another parenteral use for paraldehyde has been for an occasional patient with acute coronary thrombosis who fails to obtain relief from pain by repeated injections of morphine sulfate. In such an instance, paraldehyde has been given by intramuscular injection in doses of five to eight cc or by intravenous injection in smaller amounts. Pain occurs from intramuscular injection, but it rapidly disappears with the onset of sleep.

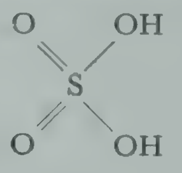
Paraldehyde has also been employed by rectal administration for obstetrical analgesia and amnesia, usually in combination with other drugs such as barbiturates and scopolamine (Kotz and Kaufman, 1939). This type of anesthesia should be employed only by those thoroughly familiar with the technic and dangers of the use of paraldehyde as a basal anesthetic.

Contraindications and Disadvantages. In bronchopulmonary disease, paraldehyde at times may be contraindicated because of the excretion of the drug by the lungs. Hepatic insufficiency also may be a contraindication to the use of paraldehyde (Levine and coworkers, 1939) inasmuch as approximately 80 per cent of the drug is destroyed in the body, presumably by the liver. The amount of paraldehyde excreted by the lungs increases in the face of hepatic insufficiency. In patients with gastro-enteritis, especially if ulceration is present, paraldehyde may cause considerable irritation. One of the chief disadvantages of paraldehyde arises from the odor it imparts to the exhaled air for as long as 24 hours. The entire room may be "perfumed" by a patient who has received the drug. The patient, however, is unaware of the odor. One who must go about his daily affairs in contact with others may not thank the physician who has given him a night's sleep at the expense of the following day's embarrassment. A second disadvantage is the unpleasant taste of paraldehyde and the irritation of the throat and gastric mucosa which may ensue if the drug is not given well diluted in a proper vehicle. Finally, paraldehyde is quite toxic when combined with morphine, but such a combination can readily be avoided.

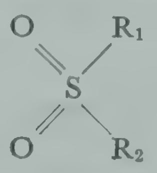
SULFONMETHANE (SULFONAL)

Historical. The ethyl sulfones were first prepared in 1885 and introduced into therapeutics by Baumann and Kast in 1888. For many years they represented the hypnotics most frequently used, but now they have been almost completely discarded.

Chemistry. The sulfones are sulfuric acid derivatives, as follows:

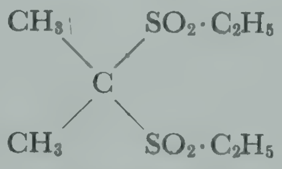


Sulfuric Acid



Sulfone

The sulfones used in therapeutics are more properly viewed as derivatives of methane. For example, sulfonmethane itself is diethylsulfone dimethylmethane, with the following structure:



Sulfonmethane

Sulfonmethane is a nearly tasteless, colorless, crystalline powder, which is almost insoluble in water (1:450), but soluble in boiling water to the extent of 1:15. The hypnotic action of sulfonmethane is largely resident in the ethyl radicals, and is increased by substituting one or both methyl groups with ethyl, to form sulfonethylmethane and sulfondiethylmethane, respectively.

Pharmacological Actions. Sulfonmethane is a fairly powerful hypnotic, but a weak analgesic. Sulfonmethane is absorbed very slowly from the intestinal tract and hence its effects are tardy in appearing. In fact, sedation or sleep may not appear for from two to five hours or more after administration. One is therefore at a loss to predict the hypnotic effects or to know exactly when to give the drug in relation to bedtime. Sleep, once induced, continues for six to eight hours.

Sulfonmethane is also slowly excreted, and after-depression upon awakening is marked. This consists of lassitude, dizziness, and mental depression and may be so pronounced that the patient is often inclined to sleep on the night of the second day without necessity for hypnotic medication.

Excretion. Excretion of sulfonmethane occurs slowly in the urine. Some of the chemical is also eliminated through the intestines, and a small amount by way of the skin. The drug is excreted partly unchanged, and partly as ethylsulfonic acid which has no depressant action. A period of several days is required for the complete elimination of a single therapeutic dose.

Toxicology. A single therapeutic dose of sulfonmethane affects neither circulation nor respiration, and the margin of safety is ample. However, this holds true only for discontinuous administration. Because of the slow rate of excretion of sulfonmethane, cumulative toxic effects and serious poisoning occur if administration is continued for any length of time. The drug is therefore obviously unsuitable for repeated or chronic use.

Acute poisoning results from overdosage, and is characterized by deep sleep and gradual failure of the respiration and circulation. Death or recovery occurs after prolonged coma. A single dose of from five to 30 grams occasionally may cause acute poisoning, but recovery has followed the ingestion of 100 grams.

Chronic poisoning occurs only after several weeks of daily therapeutic doses of sulfonmethane. The patient slowly develops symptoms referable to the nervous system—paresis, ataxia, mental depression, polyneuritis, muscle cramps; symptoms referable to the gastrointestinal tract—vomiting, periumbilical pains, tympanites, diarrhea or constipation; and urinary changes with the presence in the urine of methemoglobin, hematoporphyrin, casts and red blood cells. Hematoporphyrin, when present, is characteristic of chronic poisoning by sulfonmethane. It imparts a dark cherry-red color to the urine which is black in reflected light. Cutaneous eruptions may occur, and fatty degeneration of the liver and acute glomerulonephritis sometimes result. The blood may contain detectable amounts of sulfhemoglobin, methemoglobin and hematoporphyrin. Death occurs several weeks after the appearance of symptoms, and is preceded by terminal anuria, collapse and coma. Recovery ensues slowly if the drug is stopped when the degree of poisoning is still mild; but if the urinary changes described have already appeared, the prognosis is grave.

Preparations and Doses. *Sulfonmethane* (Sulfonal) N.F., B.P., is given in the usual soporific dose of 0.75 to 1.0 gram, but as much as 2.0 grams may be taken at once. The drug can be dispensed in capsules, as a powder, or in hot milk or other hot drinks, and should be ingested at least three to four hours before retiring. Because of the danger of cumulative toxic effects, daily doses should not be prescribed continuously for more than one week at a time. Sulfonmethane is rarely prescribed.

SULFONETHYLMETHANE (TRIONAL)

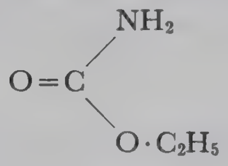
Sulfonethylmethane is chemically similar to sulfonmethane, an ethyl group in the former compound replacing one of the methyl radicals of the latter. This enhances the hypnotic potency. *Sulfonethylmethane* is official in the U.S.P. It is a colorless, odorless, bitter crystalline powder which is soluble in alcohol, but only slightly soluble in water (1:200). Sulfonethylmethane, however, is more soluble and more quickly absorbed than sulfonmethane. Nevertheless, it requires from one-half to one hour or longer to produce sedation or sleep. The drug has the uses and dangers of sulfonmethane, but is to be preferred to the latter. The single soporific dose is 0.75 to 1.3 gram, best administered in hot milk or other hot drinks. The drug is rarely used.

SULFONDIETHYLMETHANE (TETRONAL)

Sulfondiethylmethane differs from sulfonmethane in that both methyl groups in the latter compound are replaced by ethyl radicals. It is therefore considerably more powerful as an hypnotic than is sulfonmethane; but it is even less soluble. Consequently the drug is much too slow in its onset of action to be of clinical use. One is never certain in giving sulfondiethylmethane whether its effects will be manifest on that day or the day following.

URETHANE

Urethane (Ethyl Carbamate), N.F., has the following structural formula:



Urethane

It is closely related chemically to urea and carbromal and consists of colorless crystals which are very soluble in water and alcohol. The *hypnotic action* of urethane in man is feeble but it is rapid and potent in animals. Urethane is thus used chiefly as a laboratory anesthetic. It is oxidized in the body to carbon dioxide and urea and is non-toxic in therapeutic doses. The adult hypnotic dose is two to four grams, but the drug is seldom used. Urethane is combined with quinine hydrochloride as a *sclerosing solution* for the injection treatment of varicose veins (page 912).

Various urethane derivatives have from time to time been employed as hypnotics, such as *aponal* and *hedonal*. The latter, for example, is obtained by substituting the radical methyl propyl carbinol for the ethyl group of urethane, to yield the following structure: $NH_2 \cdot CO \cdot O \cdot CH(CH_3)CH_2CH_2CH_3$. Hedonal is more depressant and more toxic than urethane and its use is not advised.

BULBOCAPNINE

This interesting alkaloid is discussed here not because it is used clinically as a central depressant, but rather for the reason that its main action, depression of certain functions of the brain stem, permits no other classification. *Bulbocapnine* is derived from tubers of the *Corydalis bulbosa* or *cava* plant, commonly known as "Dutchman's breeches." Chemically, the alkaloid bears a striking resemblance to apomorphine. Two interesting points arise in this connection. First, the slight difference in chemical structure of bulbocapnine divests it of the emetic action so characteristic of apomorphine. Second, some species of *Corydalis* are closely related to the poppy family and contain chemical substances which have not been investigated. As long ago as 1526, bulbocapnine was recommended for diseases of the head and nerves, and for trembling of the hands, and it has been used sporadically for tremor up to the present time. The history of the drug has been reviewed by de Jong and Schaltenbrand (1924).

Actions. The administration of bulbocapnine to animals results in a peculiar state of catalepsy. This was first described in cats by Peters in 1904, and since then has been demonstrated for nearly all species studied. When a dose of 40 mgm per kg is injected subcutaneously into a cat, there occurs in about ten minutes a "fixed posture" which is maintained for several hours. Voluntary motion is absent, and a peculiar plastic rigidity ensues which allows the animal to be bent like a lead pipe, and placed in many bizarre positions. Some degree of sedation and lethargy is also noted, especially in rabbits and guinea pigs. Recovery with no after-effects is complete within 18 hours. When larger doses are given, tonic and clonic convulsions appear, and death may follow.

Electromyograms show the skeletal muscles to be entirely normal during the rigid state and the site of action is therefore believed to be central. Whether the phenomenon of plasticity is due to simultaneous contraction of antagonistic muscles or to some other disturbance of reciprocal innervation is not clear. The effect of bulbocapnine on the grasp reflex and hanging response in monkeys and the bearing of this on flexor tone and catalepsy were investigated by Richter and Paterson (1931). Cocaine counteracts the catatonia, especially in monkeys (Buchman and Richter, 1933), and scopolamine enhances it. Other pharmacological actions of bulbocapnine thus far described are of no immediate interest.

Use and Status. Bulbocapnine has greater academic than clinical importance. It has sporadically been tried for the control of tremor in paralysis agitans and Parkinson's disease with varying success. The drug seems to be less effective than scopolamine and has not gained wide favor. It has also been employed in encephalitis and chorea but the reports of success are highly questionable. The dose for an adult human being is 200 mgm given orally. A dose of 500 mgm may cause moderate drowsiness. No cumulative or toxic effects appear even after several months of medication. Bulbocapnine has remained a pharmacological curiosity and is employed chiefly as a means of studying cataleptoid states in animals and to immobilize the latter for other purposes.

CANNABIS

History and Source. Cannabis is obtained from the flowering tops of hemp plants. These grow wild in many parts of the world and are indigenous to the United States. The cultivation of hemp plants for commercial purposes is under the regulatory control of the Federal Government. Cannabis is now listed separately as a narcotic.*

Cannabis is a very ancient drug, and was used in the Orient before the time of written history. It is described in a Chinese herbal of the fifth century B.C. Other names for it include *hashish, marihuana* and *bhang*. The term *hashishan* is Arabic for herb-eaters. There is some dispute as to whether the English word "assassin" is derived from "hashish." The term "marihuana" is said to be a corruption of the Portuguese word "maraguango," meaning intoxicant. The drug is habitually used for its psychic effects by millions of people in all parts of the world; preparations of it are smoked, chewed or drunk.

Hemp has considerable commercial value. The fibers are used for twine, rope, bags and clothing. The seeds yield an oil which is employed in paints, varnishes and linoleum. The seeds themselves are even eaten as a gruel in the Orient in times of food shortage.

Active Principle. The source of the official U.S.P. *Cannabis* is from *Cannabis sativa*. Little is known concerning the active principle of cannabis except that it is not an alkaloid. A red syrupy oil called *cannabinol* obtained by vacuum distillation has been found to contain a highly active substance. Cannabinol is soluble in alcohol but not in water.

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* Narcotic-Internal Revenue Regulations Relating to the Importation, Manufacture, Production, Compounding, Sale, Dealing In, Dispensing, Prescribing, Administering and Giving Away of Marihuana. U. S. Government Printing Office, Washington, D. C., 1937. Price, 10 cents

and is variously said to be a diterpene or dibenzopyran structure. It is excreted from the body through the kidneys in combination with glycuronic acid. Standardized preparations of cannabis are difficult to obtain and differ widely in their potency. Besides cannabis itself, which is the dried flowering plant top, the *Extract of Cannabis* (dose 15 mgm) and the *Fluidextract of Cannabis* (dose 0.1 cc) are official U.S.P. drugs. The chemistry of various fractions of cannabis has been reviewed in the monograph by Walton (1938).

Freshly extracted cannabis possesses a brilliant green color which results from its content of chlorophyll. This extract has been employed to color corn medicines green.

Actions of Cannabis. The effects of cannabis manifest themselves almost entirely on the central nervous system. The psychic changes brought about by the drug are particularly interesting and have formed the subject of many works of fiction. The actions have been studied by pharmacologists and psychiatrists alike. A particularly fascinating older description of the actions of cannabis is given by Wood who himself took an overdose and reported his experiences (Wood, 1869).

The central effects of the drug combine elements of excitation and depression, and vary with the personality of the individual, the route of administration, and the species and potency of the cannabis. The commonest method of using the drug in the United States is to smoke it in the form of cigarettes which are known as "reefers." These are shorter and thicker than the common cigarette, are wrapped in brown paper and are sold illicitly. The smoking of two to three reefers usually brings on the desired effect.

Soon after taking cannabis the subject finds himself in a dreamy state of partial consciousness in which his ideas are disconnected, uncontrollable and plentiful. At times, there is a feeling of extreme well-being, exaltation, excitement and inner joyousness. At other times, the subject may sink into a moody revery, or experience panic-states and fear of death. Ideas come in disrupted sequences, things long forgotten are remembered and others well known cannot be recalled, imagination runs riot, and perception is crowded and disturbed. Minutes seem to be hours, and seconds seem minutes. Even space may be broadened and near objects may appear far distant. The head often feels swollen and the extremities feel light and lengthened. Extremely vivid hallucinations are experienced; these are often very pleasant and may have sexual coloring. Illusions are also common, and the feeling of being a dual personality may occur. Behavior is impulsive, mood is elevated and random ideas are quickly translated into action in the motor field.

Delirium and mania can ensue, and violent acts have been committed under the influence of cannabis. Suicide, homicide and sexual assaults have been blamed on the use of the drug, but the evidence is not always of the most acceptable variety. Inasmuch as inhibitions are removed by cannabis and personality traits thereby exaggerated, the criminal is perhaps emboldened to do violence. The psychiatric and criminological aspects of the use of marihuana have been well reviewed by Bromberg (1939).

Central depression also results in anesthesia of the skin, and the modalities of pain and touch are especially obtunded. Hearing, however, may be intensified for some time. Large doses eventually produce sleep, but the psychological effects may persist upon awakening for 24 hours and longer. The drug is said to have some diuretic action.

Addiction and Habituation. Addiction to cannabis does not occur in the same sense as it does to morphine, but habituation develops. Discontinuance is therefore easier and does not entail the sequence of profound psychic and organic symptoms seen in morphine withdrawal (Bromberg, 1934, 1939; Yawger, 1938). Although cannabis may be considered a habit-forming drug in the sense that its devotees continue to take it to experience again and again the sensations and feelings which the drug produces, true addiction cannot be said to exist. Also, tolerance, so far as is known, does not develop. There are no recognizable lasting ill effects from the acute use of marihuana, and fatalities do not occur.

The prolonged use of the drug in psychopathic personalities may eventually result in mental deterioration, a fact known for centuries in Egypt and the Orient. Chronic dementia and deterioration, however, have not been reported from American clinics. Cannabis has also been considered as a breeder of crime in psychopathic individuals, a concept supported by the acts of violence presumably committed while under the acute toxic influence of the drug. However, from a study of 67 cases involving marihuana observed in the Psychiatric Clinic of the Court of General Sessions, New York County, Bromberg (1939) reported that no positive relation could be found between violent crime and use of the drug. No cases of murder or sexual crimes due to marihuana were established.

In many large cities there are clubs or dens where marihuana users congregate for smoking and mating. It is difficult to appraise the extent of the marihuana habit and the few reliable statistics available are at odds with the impression one gains from reading the newspaper headlines. The law enforcement agencies give the opinion that marihuana smoking is spreading among the younger age groups, especially high school students. Steps have been taken by the Federal Government to control the cultivation of hemp, but this is difficult because the plant grows wild in yards and by the roadside. The illicit sale of reefers is the source of the main supply of cannabis to the laity.

Uses. Cannabis has no rational or indispensable uses in modern medicine. While it was formerly employed empirically in migraine, insomnia, neuralgia and many other syndromes, it is now no longer prescribed.

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CHAPTER 12

MORPHINE AND OTHER OPIUM ALKALOIDS

In 1680 Sydenham wrote, "Among the remedies which it has pleased Almighty God to give to man to relieve his sufferings, none is so universal and so efficacious as opium." This appraisal is still true today. If it were necessary to restrict the choice of drugs to a very few, the great majority of physicians would place the opium alkaloids, particularly morphine, at the head of the list. Morphine is unequalled as an analgesic and its indispensable employment in medicine and surgery is well defined.

History. The word "opium" is derived from the Greek word for juice, the drug being obtained from the juice of the poppy capsules; the term "codeine" comes from the Greek for poppy head. Thebaine, another natural alkaloid of opium, obtains its name from the Egyptian town of Thebes where a certain type of opium was produced. "Thebaicum" has survived as another name for opium.

The poppy plant is indigenous to Asia Minor. From there the use of opium spread to Greece. Although opium was used before history was recorded, the first undisputed reference to poppy juice is found in the writings of Theophrastus in the third century B.C. He called opium "meconion" and the synonym "meconium" has persisted to this day. Dioscorides in the first century A.D. was fully acquainted with the method for the collection and preparation of opium and his directions for preparing syrup of poppy, "dia-kodion," are essentially unchanged in modern pharmacopeias.

Arabian physicians were well versed in the uses of opium. The introduction of the drug to the Orient and China was accomplished by Arabian traders. The Chinese employed opium mainly for the control of dysenteries. The spread of the opium habit throughout China did not occur until the latter part of the eighteenth century when the Portuguese and later the English started to exploit the natives in this regard. The war against opium has continued ever since and at times has resulted in armed conflict.

By the middle of the sixteenth century, the uses of opium which are valid today were fairly well understood in Europe. Paracelsus called opium the "stone of immortality" and leaned heavily on its employment in his medical practice. To him is accredited the compounding of tincture of opium or "laudanum" which is an official preparation today. Von Helmont, a contemporary of Sydenham, was called Doctor Opiatus because he prescribed opium so frequently. Paregoric, another pharmacopeial mixture, dates from an elixir for asthma first prepared in the early eighteenth century by Le Mort, the chemistry professor at Leyden. The word paregoric comes from the Greek term for "soothing." Dover's powder is another opium-containing drug which has survived through the years. It is named for the famous English adventurer and physician, Thomas Dover, who introduced the powder as a sweating agent for gout in 1732. Dover is probably better remembered as the rescuer of Selkirk, characterized in fiction as Robinson Crusoe. The "brown mixture," opium and licorice, is named for its color and not its originator, Dr. Barton of Philadelphia (1814).

Until well into the 19th century the only opium preparations used medicinally were crude extracts. In 1805, a young German pharmacist in Hanover named Sertürner isolated and described morphine. This epochal finding went unnoticed until his later publication in 1816. Sertürner almost lost his life by experimenting with morphine on himself. The discovery of other alkaloids in opium quickly followed that of morphine and the use of pure alkaloids rather than crude preparations soon spread throughout the medical world. Codeine was isolated by Robiquet in 1832 and papaverine by Merck in 1848. One interested in the history of opium is referred to the interesting account given by Macht (1915).

Source and Composition of Opium. Opium is obtained from the milky exudate of the incised unripe seed capsules of the poppy plant, *Papaver somniferum,* which is indigenous to Asia Minor. The opium poppy is cultivated in other countries including Egypt, India, China and Persia. The milky juice is dried in the air and forms a brownish gummy mass. This is further dried and powdered to make the official powdered opium.

The pharmacologically active constituents of opium are alkaloids. These number well over a score but only three—morphine, codeine, and papaverine—have wide clinical use. In addition to alkaloids, opium contains a large number of chemical substances which do not contribute to the pharmacodynamic properties of the drug. These are organic acids, resins, gums, oils, sugars and protein-like bodies, and comprise about 75 per cent by weight of opium.

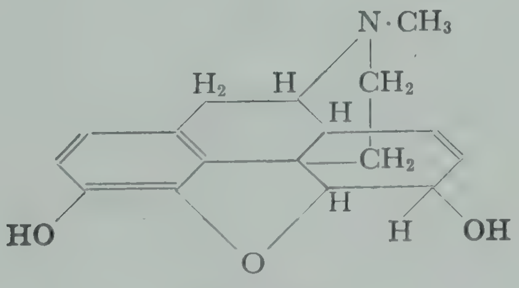
The alkaloids form about 25 per cent by weight of the opium. They may be divided into two distinct chemical classes—the *phenanthrene* and the *benzylisoquinoline* derivatives. These groups contrast sharply in their pharmacological properties. The main alkaloids of medical interest which occur naturally in opium and their approximate percentages are shown in Table 7. The many other natural alkaloids of opium occur in such small amounts and contribute so little to its actions that they are omitted from discussion. They are not readily available and have no clinical uses.

TABLE 7

THE ALKALOIDS OF OPIUM

GROUP	NATURAL ALKALOID	PERCENTAGE IN OPIUM
1. *Phenanthrene*	Morphine	10.0 (3 to 23)
	Codeine	0.5 (0.2 to 0.8)
	Thebaine	0.2 (0.2 to 1.0)
2. *Benzylisoquinoline*	Papaverine	1.0 (0.5 to 1.0)
	Narcotine	6.0 (0.75 to 10.0)
	Narceine	0.3 (0.1 to 0.5)

Chemistry of the Opium Alkaloids. Morphine is by far the most important phenanthrene alkaloid of opium and gives to the latter its predominant pharmacological characteristics. The exact structural formula of morphine has been the subject of considerable chemical research (*see* Small, 1932). The formula most commonly accepted today is that of Gulland and Robinson (1925) which is the following:



Morphine

This formula, while not yet entirely proved, accounts for more of the complicated facts of morphine chemistry than does any other. The morphine molecule can be seen to consist of a partially hydrogenated phenanthrene nucleus, an oxide bridge, a nitrogen containing chain, ethenamine $(—CH_2CH_2N(CH_3)—)$, attached in a very unusual way to the phenanthrene nucleus and constituting a part of a six-membered heterocyclic ring, and two hydroxy groups.

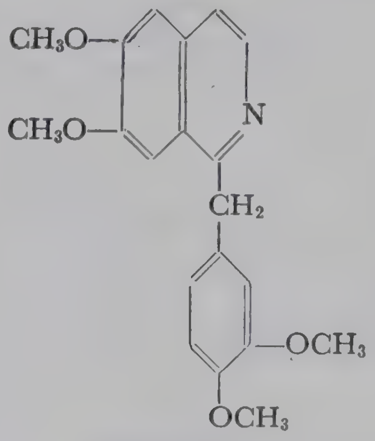
In the formula, the two hydroxy groups which are of basic importance for the actions of morphine are shown in bold-faced type. They are known as the *phenolic* and *alcoholic* hydroxy groups. Morphine has not been synthesized in the laboratory but many of its derivatives are made by the introduction of relatively simple chemical radicals into the hydroxy groups of the morphine molecule. Many of the naturally occurring phenanthrene alkaloids differ from morphine only by virtue of substituted radicals in one or both of these OH groups.

For example, *codeine* is methylmorphine, the methyl substitution being on the phenolic OH. If both hydroxy groups of morphine have methyl radicals inserted, dimethylmorphine or *thebaine* is formed. *Dionine,* a synthetic alkaloid, is produced by replacing the phenolic OH with an ethoxy group to form ethylmorphine. Diacetylmorphine or *heroine* (heroin) is another synthetic morphine derivative made by the acetylation of both OH groups. Dihydromorphinone, known as *dilaudid,* is formed by replacing the alcoholic OH with a ketonic oxygen and by hydrogenation to remove the adjacent double bonds. If the empirical formula of morphine is written as $HO \cdot C_{17}H_{17}ON \cdot OH$ with the phenolic OH on the left and the alcoholic OH on the right, the structures of the more important natural and synthetic phenanthrene alkaloids of opium can be represented in a simple manner as follows:

Natural alkaloids	*Synthetic alkaloids*
Morphine $HO \cdot C_{17}H_{17}ON \cdot OH$	Heroine $CH_3CO \cdot O \cdot C_{17}H_{17}ON \cdot O \cdot OCCH_3$
Codeine $CH_3O \cdot C_{17}H_{17}ON \cdot OH$	Dionine $CH_3CH_2O \cdot C_{17}H_{17}ON \cdot OH$
Thebaine $CH_3O \cdot C_{17}H_{17}ON \cdot OCH_3$	Dilaudid $HO \cdot C_{17}H_{19}ON{:}O$

Apomorphine is yet another synthetic alkaloid obtained by vigorous treatment of morphine with strong mineral acids to cause fundamental changes in the molecule. The oxygen bridge and the internal linkage of the N-containing chain are removed to give the structural formula presented on page 813.

Papaverine, the main alkaloid of the benzylisoquinoline group, is chemically and pharmacologically distinct from morphine and its related derivatives. The structural formula of papaverine is as follows:



Papaverine

Relationship between Chemical Constitution and Pharmacological Action. The phenanthrene alkaloids act chiefly on the central nervous system where a combination of depressant and stimulant effects is produced. The only other important action is on smooth muscle which is stimulated to contract. The benzylisoquinoline alkaloids are in sharp contrast by having only insignificant effects on the nervous system and a definitely antispasmodic action on smooth muscle. When opium is given, the actions of the phenanthrene alkaloids and especially those of morphine predominate.

As a result of careful study of the actions of morphine and its derivatives, definite pharmacodynamic properties have come to be assigned to each of its two hydroxy groups. The masking of the phenolic OH in morphine, as occurs in codeine, decreases the analgesic, respiratory, depressant and intestinal spasmodic actions, but the stimulant effects on the central nervous system are enhanced. Therefore compounds such as codeine and thebaine are much less narcotic than morphine and in large doses may produce convulsions, especially in certain species of animals which are susceptible to stimulatory effects of morphine and its derivatives. Indeed, thebaine can produce strychnine-like convulsions and should be classed with the central stimulants. On the other hand, when the alcoholic OH is masked, as by the introduction of an acetyl group to form heroine or by replacement with a ketonic oxygen to form dihydromorphinone (dilaudid), the narcotic and respiratory depressant properties of morphine are exaggerated. This is especially true if the alcoholic hydroxy group is entirely eliminated, as in the desoxymorphine compounds. When either the phenolic or alcoholic OH's are masked, the convulsant effects, as a rule, are increased and the emetic action is decreased.

From these basic facts, it would appear that the free phenolic OH in morphine is the basis for the analgesia, hypnosis, respiratory depression and constipation, and that the free alcoholic OH tends to counteract these effects. The integrity of both hydroxy groups is essential for a relative absence of excitatory phenomena. Thus codeine is more convulsant than morphine; heroine, though more narcotic than morphine, also produces greater stimulation of the nervous system. The emetic properties of morphine likewise appear to be connected with the free OH's and if either one of the hydroxy groups is masked, vomiting is less pronounced.

TABLE 8

EFFECTIVE DOSES IN MILLIGRAMS PER KILOGRAM OF ALKALOIDAL BASE

	CODEINE	MORPHINE	DILAUDID
Average Fatal Dose (mice)	241 *	531	84
Convulsions (mice)	161	531	67
General Depression (rats)	36.1	6.75	0.88
Analgesia (cats)	8.04	0.75	0.17
Respiratory Depression (rabbits)	1.3	0.15	0.011
Emetic Action (cats)	16.0 **	0.22	0.08
Exciting effect (cats)	8.04	0.57	0.17

* The lower toxicity of morphine as compared with codeine holds only for animals which are quite susceptible to the convulsant effects of these derivatives. Thus codeine is more toxic for mice although morphine is more lethal for man.

** Vomiting did not occur with any dose used; nausea (licking, with or without salivation) seen at dose indicated.

Compiled from data presented by Small, Eddy, Mosettig and Himmelsbach (1938).

In Table 8, compiled from the data presented by Small, Eddy, Mosettig, Himmelsbach and associates (1938), the differences between morphine (two free OH's), codeine (masked phenolic OH) and dihydromorphinone [dilaudid] (change in the configuration of the alcoholic OH) are clearly seen.

Other fundamental features of the morphine molecule have also been investigated. This work has largely been the result of an extensive cooperative research program, initiated in 1928 and still in progress, undertaken jointly by a number of chemists and pharmacologists under the auspices of the National Research Council, the Universities of Virginia and Michigan, the Rockefeller Foundation and the Narcotic Bureau of the United States Public Health Service. The object is ultimately to find potent analgesic substitutes for morphine which do not cause addiction and lack certain other undesirable properties. Scores of compounds have been investigated and the relation between chemical structure and certain definite pharmacological actions has been elucidated. The properties particularly studied are analgesia, depression, emesis, intestinal stimulation, respiratory depression, excitatory phenomena, and potentiality for causing addiction.

Not only have synthetic morphine derivatives, numbering over 125 compounds, been investigated, but also compounds simpler than morphine, yet resembling it in respect to certain features, have been studied. Thus, for example, it has been found that when the ethenamine ring is opened a considerable loss of typical morphine effects results. If phenanthrene itself is injected into animals, only mild sedation occurs; but, when a phenolic OH is added in the position occupied by the phenolic OH in morphine, the hypnosis is more marked and some evidence of obtundation of pain appears. When another OH is added in the position occupied by the alcoholic OH of morphine, narcotic effects are enhanced. Numerous radicals, including an N-containing open chain similar to ethenamine, have been attached to the phenanthrene nucleus in various positions and in each instance it has been found that the position occupied by the phenolic OH in morphine is the crucial one for the elicitation of depressant and analgesic effects. Because no proof exists that phenanthrene contributes an essential part to the action of morphine, other substances synthesized from the phenanthrene, phenanthrylene oxide, phenanthridine, dibenzofuran and carbazole series have been investigated. Many of the conclusions drawn from a study of the behavior of related drugs in the morphine series would seem to be applicable to similarly related derivatives of the dibenzofuran and phenanthrene series.

Of more than academic interest is the fact that compounds which may prove clinically useful as substitutes for morphine and codeine are beginning to emerge from the extensive plan of investigation outlined. Certain coal tar derivatives have already been synthesized which in animals, at least, compare favorably with codeine as analgesics and possess no euphoric quality. To mention but one of the more promising chemicals which may be valuable as a substitute for morphine, *methyldihydromorphinone* ("metopon"), in particular, deserves brief description. It has already received considerable pharmacological and clinical study but no conclusion is as yet justified concerning development of tolerance to it or its addicting potency in comparison with morphine. Relief of pain occurs quickly after the subcutaneous injection of two to seven mgm of the drug, and analgesia lasts for more than two hours (page 196). Most important is the fact that no respiratory depression or other serious untoward result has been noted. The phenomena disclosed by substituting methyldihydromorphinone for morphine in addicts and then withdrawing the substituted drug are clearly depicted in Table 11. Further clinical work is required before it can be determined whether habituation and dependence develop after continued medication with this chemical (Himmelsbach, Eddy and associates, 1938; Himmelsbach, 1939; Eddy, 1939).

For the details of this important field of investigation the interested reader is referred especially to the papers of Eddy and collaborators (1932, *et seq.*), and to the monograph by Small, Eddy, Mosettig and Himmelsbach (1938) which also contains an extensive bibliography.

Pharmacological Actions of Morphine

When opium is administered to man, the most prominent clinical effects are discernible on the central nervous system and the bowel. Morphine is responsible for the major actions of opium and therefore its pharmacological properties will be discussed in detail. The significant variations of other alkaloids of opium from the morphine pattern of action will be presented as occasion arises.

Central Nervous System. Morphine exerts a *narcotic action* in man manifested by analgesia and sleep. A significant feature of the analgesia is that it occurs before and often without sleep. When moderate amounts of morphine are given (up to 15 mgm), human subjects soon experience an euphoric, exhilarating drowsiness characterized by freedom from anxiety, muscular relaxation, rapid flow of uncontrolled thought and imagination, shortening of the time sense, disappearance of fears, doubts and inhibitions, and increased ease of discriminating and making decisions. There is inability to concentrate, difficulty in mentation, apathy, lessened physical activity, dimness of vision, and lethargy. Pain is relieved, hunger is abolished, and vomiting (when it occurs due to morphine) is not associated with the usual unpleasant emotional reactions, even when it is violent and repeated. The respiration is depressed and the pupils are somewhat constricted. If the external situation does not prevent it, sleep soon ensues and dreams may be prominent. The psychological effects enumerated outlast the analgesic action by many hours (Wolff and coworkers, 1940). Codeine produces psychological effects similar to morphine but milder in intensity.

When full therapeutic doses of morphine are given (15 to 20 mgm), the stage of euphoria, lessened activity and mental sluggishness quickly passes into one of deep dreamless sleep from which the patient is aroused with difficulty. Severe pain is relieved as a rule; the respirations are definitely slowed; the pupils are quite constricted; and recovery is characterized by after-depression, constipation and sometimes by nausea and vomiting. As the dose of morphine is increased beyond the ordinary therapeutic amounts, all the effects mentioned become more marked. Poisoning is characterized particularly by deep coma, markedly depressed respirations and pin-point pupils. With lethal doses of morphine, death occurs from respiratory failure.

The typical course of morphine action as presented is not always evident. Many factors may modify the effects of the drug, particularly idiosyncrasy and the level of reflex excitability of the nervous system. These will be discussed later but certain features of *morphine excitation* of the nervous system are mentioned at this point. Some individuals, especially women, are excited by morphine. This effect usually does not extend beyond nausea and vomiting due to a medullary stimulation which precedes depression; but, in rare cases, delirium and even convulsions may occur. Certain morphine derivatives and natural alkaloids of opium are more likely to produce these excitatory phenomena. Thus codeine does not produce progressive depression as its dose is increased but causes marked excitement. It has already been stated that thebaine resembles strychnine more than it does morphine and can elicit convulsions. Heroine is known to cause central excitation and is taken by the heroine addict for euphoric stimulation long after tolerance to the depressant effects has occurred. Apomorphine is the most potent direct stimulant of the emetic center. The chemical basis of the excitatory properties of morphine has already been discussed.

Certain species present clearly the excitatory effects of morphine for in some animals this alkaloid causes almost pure stimulation, convulsions and death by exhaustion. In the cat, for example, morphine causes wild mania and tonic and clonic spasms which last many hours and often end fatally. Even decorticated cats respond in this manner (Hambourger, 1937) and the stimulation therefore cannot be due to a release mechanism such as operates in the excitement stage of general anesthesia. Other species, including pigs, goats, asses and horses are stimulated by morphine. The alkaloid has thus been used to stimulate horses prior to racing. The dog is depressed by morphine but initially shows restlessness, nausea, vomiting and defecation, due to preliminary central excitation.

The *central depression* produced by morphine is considerably different from that caused by the hydrocarbon inhalation anesthetics. Morphine, even in small doses, causes a selective depression of the respiratory center whereas many anesthetics are respiratory stimulants. The general anesthetics also depress the motor cortex but this is evident only after large doses of morphine. An individual may be aroused from morphine narcosis and be in full control of his motor functions. Furthermore, analgesia occurs with the anesthetic drugs only when consciousness has been clouded or lost but morphine relieves pain before and often without producing unconsciousness. Morphine differs from the sedatives such as the barbiturates in its specific analgesic power, its respiratory depressant action and its relatively poor anticonvulsant potency.

Spinal Cord. The excitatory effects of morphine are particularly evident on the medullary vomiting center and the spinal cord. In spinal animals, the alkaloid can cause strychnine-like tetanus. The ability to produce stimulation of the cord is the chief reason why morphine is not useful as a sedative agent in strychnine poisoning and other convulsive syndromes. As the cerebrospinal axis is ascended, stimulation becomes progressively less marked. These facts allow the anatomical summary that "morphine depresses from above downward and stimulates from below upward." It is thus clear that morphine produces a peculiar mixture of excitation and depression of the central nervous system.

Peripheral Nerves. The peripheral nerves and sense organs are unaffected by morphine. The former practice of applying opium plasters and ointments locally to relieve pain was based on the belief that opium acted directly on nerve endings to cause analgesia. Pain is abolished only by the central actions of morphine and the local use of opium preparations is therefore irrational and obsolete.

Respiration. Morphine is a primary and continuous depressant of respiration by virtue of a direct action on the respiratory center. The effect is discernible with small doses insufficient to produce sleep or disturb consciousness. The action is a highly selective one and the degree of depression is directly proportional to the dose. Initially, as the rate decreases, the depth of breathing may increase sufficiently to raise the respiratory minute volume. Soon, however, the depth of respiration also diminishes and the respiratory minute volume falls. After toxic amounts of morphine, the number of respirations per minute may fall to three or four and respiratory arrest is the cause of death in acute morphine poisoning. The respiratory center depressed by morphine fails to react normally to stimuli. Whereas both the rate and depth of breathing are normally increased by carbon dioxide inhalation, after morphine the depth is affected much more markedly than the rate. After small doses of morphine which cause slowing of respiration and a reduced tidal volume, the vagal reflexes affecting respiration are exaggerated, phenomena commonly seen in response to a lowered alveolar carbon dioxide concentration (V. E. Henderson and Rice, 1939). Inasmuch as the alveolar carbon dioxide concentration is elevated in morphine depression, it is likely that the cells of the respiratory center are much less sensitive to carbon dioxide (Y. Henderson, 1938). Although Henderson and Rice noted in their animal experiments that small doses of morphine caused peripheral sensory stimuli to increase respiratory rate and ventilation, toxic doses in man tend to diminish or prevent the usual acceleration of breathing caused by painful stimuli. Cheyne-Stokes respiration is sometimes seen in severe morphine poisoning (Figure 16).

In addition to depressing respiration, morphine in small doses dulls the cough reflex and in large doses abolishes it. Dyspnea is also relieved by morphine through a depression of central sensory perception. This alkaloid is indispensable in the treatment of certain forms of cardiac dyspnea, especially the type known as "cardiac asthma" caused by pulmonary edema secondary to left ventricular failure.

Codeine is less depressant to the respiration than is morphine. Furthermore, as the dose of codeine is increased, commensurate slowing of the respiratory rate does not occur. In fact, large doses of codeine tend to stimulate the brain stem. Codeine is especially useful for its action in depressing the cough reflex. Doses of codeine effective in this regard are not as constipating as morphine and lack the serious addicting property of the requisite doses of the latter drug. *Heroine* is considerably more depressant to the respiratory center than is morphine, and at one time it was rather widely employed for depression of the cough reflex. However, the danger of addiction to heroine and the tendency of even small doses (two mgm) to abolish rather than dull the cough reflex contraindicate the use of this alkaloid in respiratory disorders. Heroine has no advantages over morphine or codeine. The action of *dionine* on respiration resembles that of codeine very closely. The effect of *papaverine* on respiration is typical of the benzylisoquinoline alkaloids which cause a mild stimulation of breathing through a direct stimulation of the respiratory center. The stimulation of respiration by papaverine, however, has no therapeutic usefulness. *Opium,* because of its papaverine content, is less depressant to respiration than its morphine content would indicate.

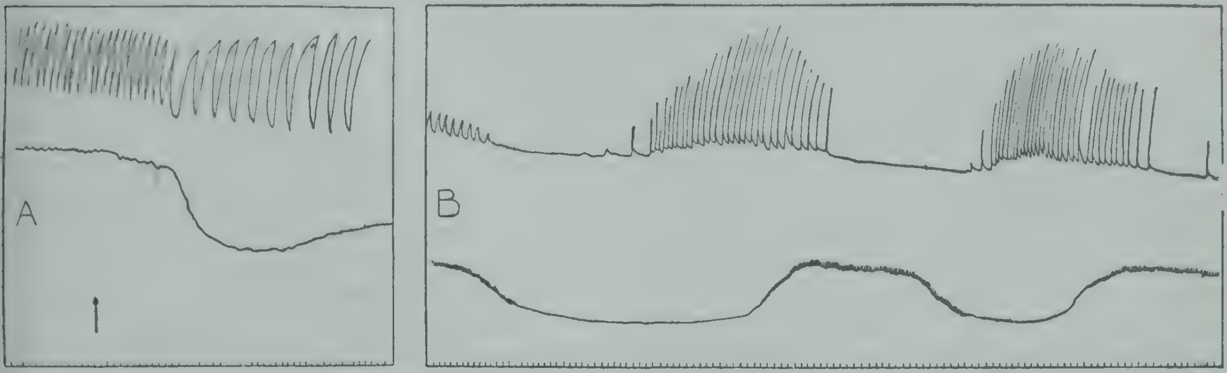


FIGURE 16. *The effect of morphine sulfate on respiration in the etherized vagotomized cat.*

Arrow indicates the intravenous injection of 10 mgm per kilogram of the alkaloid. Base line, time in five second intervals; lower tracing, blood pressure; upper tracing, respiration recorded with Cushny oncometer. *A.* The immediate effect consists in a slowing of the respiratory rate with an increase in depth. Note the fall in blood pressure following the intravenous administration of the drug. *B.* Twenty minutes later, and after total dose of 25 mgm per kg, medullary depression has led to Cheyne-Stokes respiration. Note how the periods of apnea and hyperpnea are reflected in the condition of the circulation. (After Barbour, 1914. Courtesy of the *Journal of Pharmacology and Experimental Therapeutics.*)

Pain. The relief of pain by morphine is the outstanding property of the drug and the one which clinically is most often sought. Morphine produces analgesia by a highly selective action and pain is relieved without obtundation of other modalities of sensation. The locus of this effect is entirely central and is thought to be in the optic thalami. Continuous dull pain is relieved more effectively than sharp intermittent pain. With sufficient amounts of morphine, however, it is possible to abolish nearly all forms of pain and thus morphine is the agent of choice for the severe pain of renal and biliary colic. The lightning pain of tabes dorsalis is one of the few types which resist morphine analgesia. In sharp contrast to the salicylates and related analgesics, morphine is effective against pain arising from viscera as well as from integumental structures, muscles and joints.

In a critical experimental analysis of the effects of opium alkaloids on the pain experience in man, Wolff, Hardy and Goodell (1940) have concluded that there are three components to the relief of pain afforded by opiates. First, morphine is capable of raising the threshold for pain perception. This factor operates chiefly when morphine is given *before* the painful stimulus is experienced, as when morphine is administered prior to surgical operation. When morphine is given for severe pain, the relief afforded is not due, in any large part, to the ability of morphine to elevate the pain threshold. Secondly, opiates alter the pattern of reaction to pain. This factor operates especially when the alkaloids are given for the relief of severe pain. The pain is still perceived but it no longer brings forth the usual responses (anxiety, fear, panic, withdrawal and flight). The patient is capable of tolerating the experience of pain when it is freed of its implications. This action of morphine is usually obtained within one-half hour after the drug is taken—at least one hour before the peak of the pain threshold-raising action is reached. Thirdly, opiates may induce sleep, and the investigators mentioned have determined that sleep in itself raises the threshold for pain by approximately 50 per cent.

Wolff and his associates also emphasize that there is a mutual antagonism between pain and the analgesic action of morphine and its congeners. For example, when severe pain is experienced for some time before morphine is administered, the subsequent ability of the drug to exert an analgesic action (*i.e.,* to raise the pain threshold) is limited or abolished. On the other hand, if the painful stimulus is introduced after the analgesic action of morphine has reached its peak (approximately 90 minutes after intramuscular injection), the perception of pain is less acute. These workers also observed that epinephrine, administered prior to morphine, decreased or abolished the pain threshold-raising action of the opiate. This is probably accountable for on the basis of the central excitatory effects of epinephrine (page 409), the experimental subjects having felt tense and excited long after the circulatory effects wore off. The significance of this finding arises from the fact that epinephrine is released from the adrenal medulla during pain.

Pupils. Morphine causes constriction of the pupils. The exact mechanism of the miosis is unknown. That it is central and not peripheral is indicated by the fact that local application of morphine to the eye does not affect the size of the pupil. Atropine counteracts the morphine-induced pupillary constriction. In morphine poisoning, the miosis is marked and pin-point pupils are pathognomonic. Marked dilatation occurs terminally as asphyxia intervenes. Tolerance does not develop to the miotic action of morphine. Thus the morphine addict continues to show constricted pupils.

The action of morphine on the pupil has been ascribed to a direct effect of the alkaloid on the pupilloconstrictor center (Edinger-Westphal nucleus). It may, however, result from paralysis of sympathetic pupillodilator centers in the hypothalamus. Evidence that the miosis may be due to depression of supranuclear inhibition of pupilloconstrictor tone is suggested by the fact that decortication in dogs prevents the pupillary effect of morphine. Those species which are excited by morphine usually show marked mydriasis. This is especially true in the cat. Even chronic decortication in this animal fails to prevent the pupillary dilatation following morphine.

Comparison of Opium Alkaloids in Respect to Clinical Features of Central Nervous System Depression. The members of the morphine group of alkaloids differ considerably in their degree and duration of analgesic action, the subjective depression and euphoria which they produce, and in the incidence of side-effects. All these properties are of importance to the physician in his selection of opiates. The data obtained from laboratory experiments (von Frey technic) on normal men by Seevers and Pfeiffer (1936) are particularly valuable in this respect, and the essential findings are summarized in Table 9.

That the variations in time required for peak analgesia are due to differences in the rate of absorption of the alkaloids after subcutaneous injection is indicated by the fact that after intravenous administration of the same doses peak analgesia occurred in 20 minutes with the four drugs. The investigators also found that neither the duration nor degree of analgesic action was as great after intravenous as after hypodermic medication, except for heroine which was more potent intravenously. Dilaudid, in particular, suffered a peculiar loss of efficacy after intravenous injection. Heroine was the most potent in respect to euphoria. This property was less prominent after intravenous injection, which is in contrast with the experience of the addict. The side-effects noted included nausea, vomiting, constipation, diarrhea and urticaria.

Table 9

CLINICAL COMPARISON OF CENTRAL DEPRESSANT EFFECTS OF OPIUM ALKALOIDS

Opium Alkaloid	Equivalent Analgesic Subcutaneous Doses	Time Necessary for Peak Analgesia After:		Descending Order of Potency * After Subcut. Admin. Regarding:			Untoward Side-Effects *
		Subcut. Admin.	Intrav. Admin.	Duration of Analgesic Action	Duration and Intensity of Subjective Depression	Euphoria	
	mgm	minutes	minutes				
Morphine Sulfate	10	60–90	20	1	1	2	1
Heroine Hydrochloride	1.0–2.0	30	20	4	3	1	4
Dilaudid Hydrochloride	0.8–1.0	90	20	2	2	3	2
Codeine Phosphate	64	30–60	20	3	4	4	3

Compiled from the data of Seevers and Pfeiffer (1936).
* Order of Potency: 1 =most; 4 =least.

Inasmuch as equivalent analgesic doses of the alkaloids caused varying degrees of subjective depression, it is clear that the mechanism of relief of pain is different from that of stupefaction. This conclusion is supported by the fact that maximal subjective depression occurred within five minutes after intravenous medication whereas the analgesic peak came 15 minutes later. Furthermore, after subcutaneous injection, analgesia often wore off before stupefaction became prominent. This differentiation between the mechanisms of analgesia and subjective depression is clearly seen in the barbiturates which are excellent somnifacients and poor analgesics. Scopolamine also elicits marked depression without analgesia. Conversely, the salicylates produce analgesia without stupefaction. The importance of this point rests in the fact that it is thus hopeful to search for morphine substitutes which will produce a maximum of analgesia and a minimum of subjective depression. Patients then need not be put to sleep in order to obtain relief from pain. Likewise, an investigation of 65 morphine derivatives with respect to their toxicity (mice), and their potencies as respiratory depressants (rabbits) and analgesics (cats) shows that these properties are dissociated (Sumwalt, 1938). This strengthens the conviction that synthetic morphine derivatives will be found which are satisfactory analgesics but do not cause respiratory depression.

The data of Seevers and Pfeiffer (summarized in Table 9) have been confirmed and extended, in all important respects, by the experiments of Wolff and coworkers (1940), some of whose conclusions have already been presented. These investigators devised a technic for measuring the pain threshold in man by means of a heat lamp focused on the skin of the forehead (Hardy, Wolff and Goodell, 1940). The peak analgesic action of doses of *morphine sulfate* (0.5 to 15 mgm) administered intramuscularly was reached in 90 minutes. The maximal analgesic effect of morphine proved to be a straight line function of the dose in the range between 0.5 and 15 mgm, but the increment of increase in pain threshold-raising action became progressively less as the 15 mgm amount was exceeded. Thus, the pain threshold was elevated 10 per cent by 0.5 mgm, 32 per cent by 5.0 mgm, 47 per cent by 8.0 mgm, 71 per cent by 15 mgm, but only 93 per cent by 30 mgm. The duration of the action on the pain threshold was three hours for 0.5 mgm, four hours for 2.0 mgm, over six hours for 8.0 mgm, slightly under seven hours for 15 mgm, and slightly over seven hours for 30 mgm.

With respect to *codeine,* the above investigators found that regardless of the amount injected (intramuscularly), the maximum pain threshold-raising effect was reached in approximately 90 minutes. The duration of action persisted approximately three hours with doses of 15 mgm, more than five hours with doses of 120 mgm. The threshold-raising action was proportional to the dose up to 60 mgm. Amounts larger than 60 mgm failed to cause any additional increase in pain threshold. For example, the threshold was elevated 20 per cent by 15 mgm of codeine, 30 per cent by 30 mgm, and 50 per cent by 60 mgm; but even 240 mgm failed to increase the threshold beyond 50 per cent. It is thus clear that there is little object in exceeding the dose level of 60 mgm. When codeine is compared with morphine, a 15 mgm dose of the former is equivalent to two mgm of the latter in being capable of increasing the pain threshold by 20 per cent; 60 mgm of codeine equals eight mgm of morphine in that each elevates the threshold by 50 per cent; but, as stated, additional amounts of codeine cause no further increase in threshold.

With regard to *dihydromorphinone hydrochloride* (dilaudid), it was established that a three mgm dose injected intramuscularly elevated the pain threshold 100 per cent (equivalent to 30 mgm of morphine). *Pantopium hydrochloride* (page 208) given parenterally in the dose of 20 mgm raised the pain threshold 35 per cent (equivalent to eight mgm of morphine, approximately). *Methyldihydromorphinone* ("metopon") injected in the dose of 6.6 mgm increased the pain threshold by 90 per cent (comparable to 30 mgm of morphine). The peak effect appeared in 90 minutes and remained for one and one-half hours, the control level again being reached after seven hours. Vomiting occurred and the pupils were constricted. The subjects were unable to differentiate the psychological and physiological effects of metopon (6.6 mgm) from those caused by morphine (30 mgm) or dilaudid (three mgm), but the sequelae were of shorter duration.

Smooth Muscles. The second important locus of action of the opium alkaloids is on certain smooth muscles. The phenanthrene derivatives contrast with the benzylisoquinoline drugs in that they cause contraction of smooth muscle whereas the papaverine group produces relaxation. Morphine, for example, tends to cause contraction of smooth muscles with the notable exception of those of the blood vessels. Papaverine, however, produces muscular relaxation, particularly in blood vessels.

Gastro-intestinal Tract. The *constipating effect* of opium was utilized by the the Ancients. The use of opium preparations by the Chinese for relief of diarrheas and dysenteries preceded by many centuries their employment for central depression. The typical action of opium on the bowel is due mainly to morphine. The antispasmodic action of the benzylisoquinoline alkaloids is quite weak. For clinical purposes, therefore, opium and morphine may be viewed as acting similarly on the enteric tract.

The experimental and clinical research on the complex actions of opium alkaloids on the bowel has been quite extensive. The results vary considerably and this may be attributed to differences in experimental technics. From the mass of available evidence, certain effects of morphine on the digestive apparatus appear definitely to be established. A most important conclusion is that these phenomena are due entirely to local actions of the alkaloid on the bowel and not to any effect on the central nervous system. The interested reader is referred for details to the review of this subject by Krueger (1937).

Stomach. Morphine causes an initial retardation of secretion of hydrochloric acid by the stomach. Gastric motility is also lessened and the tone of the antral portion of the stomach is increased. In addition, the pyloric sphincter is contracted. The result of these effects of morphine is to cause a slowing of the passage of gastric contents into the duodenum. This delay in the stomach may last for 12 hours or more, and contributes about one-half to the total gastro-intestinal delay which is the basis of morphine constipation. Resection of the extrinsic gastric nerves and the administration of atropine have little influence on these actions of morphine on the stomach; but in man, atropine can be shown to inhibit the increase in gastric tone caused by morphine (Veach, 1937) (Figure 17).

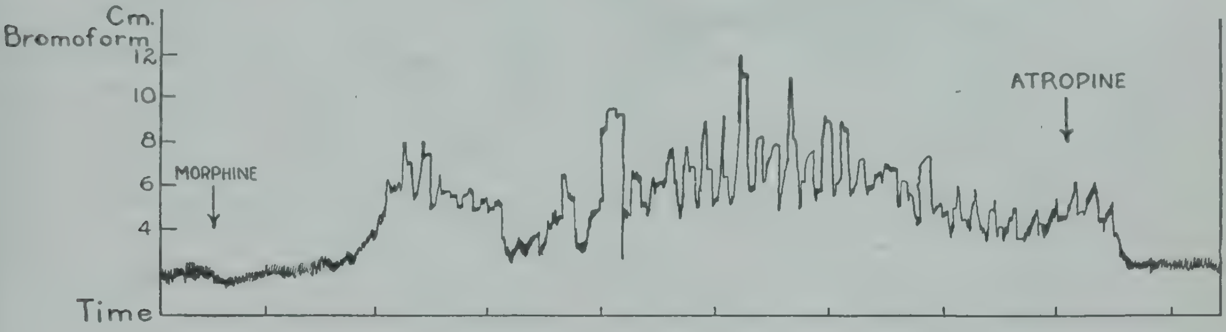


Figure 17. *The effect of morphine on the motility of the empty, intact, normal human stomach.*

Gastric motility recorded by means of a balloon connected to a bromoform manometer. Time, in units of 2.1 minutes. The intravenous injection of 7.5 mgm of morphine sulfate produced a gradual increase in tonus and in frequency of rhythmic contractions. The intravenous injection of 0.3 mgm of atropine sulfate completely abolished the rhythmic contractions and diminished the tonus. (After Veach, 1937. Courtesy of the *Journal of Pharmacology and Experimental Therapeutics.*)

Small Intestine. Both biliary and pancreatic secretions are diminished by morphine and digestion of food in the small intestine is delayed. Propulsive movements of the small bowel are interfered with by the alkaloid chiefly as a result of an increased muscular tone. Water is more completely absorbed from the chyme due to the delayed passage of the bowel contents. The viscosity of the chyme is thus greater than normal and further delay occurs. The tone of the ileocecal valve is also increased. Large doses of atropine may counteract in part the intestinal responses to morphine. These features of morphine action on the small intestine combine to cause about one-third to one-fourth of the total constipating effect of the alkaloid.

Large Intestine. Peristaltic waves in the colon disappear after morphine and the tone of the musculature of the large bowel is increased to the point of spasm. The resulting delay in the passage of the contents causes considerable desiccation of the feces which in turn prevents their advance along the colon. The tone of the anal sphincter is greatly augmented and this, combined with inattention to the normal sensory stimuli for the defecation reflex, contributes to morphine constipation. Unawareness of the necessity to defecate is due to the action of morphine on the perceptual functions of the cortex and is the only factor contributed by the central effects of the drug. The relative importance of this factor cannot easily be determined. At times, especially with the use of larger doses of opiates, it must be considerable. Omitting this factor, however, the other features of morphine action on the large intestine combine to contribute about one-quarter of the entire constipating effect.

Codeine is definitely less constipating than morphine. *Heroine* when given in equi-analgesic amounts has very little gastro-intestinal effect but in larger stupefacient doses, it does produce constipation. *Dilaudid* also appears to be less constipating than morphine. *Papaverine* and the benzylisoquinoline alkaloids tend to relax the intestinal musculature (Figure 18). This action is relatively weak, however, and when opium is administered the papaverine content is insufficient to offset the constipating effects of morphine. The addict does not develop tolerance to the actions of morphine on the bowel and he continues to suffer from alternating constipation and diarrhea.

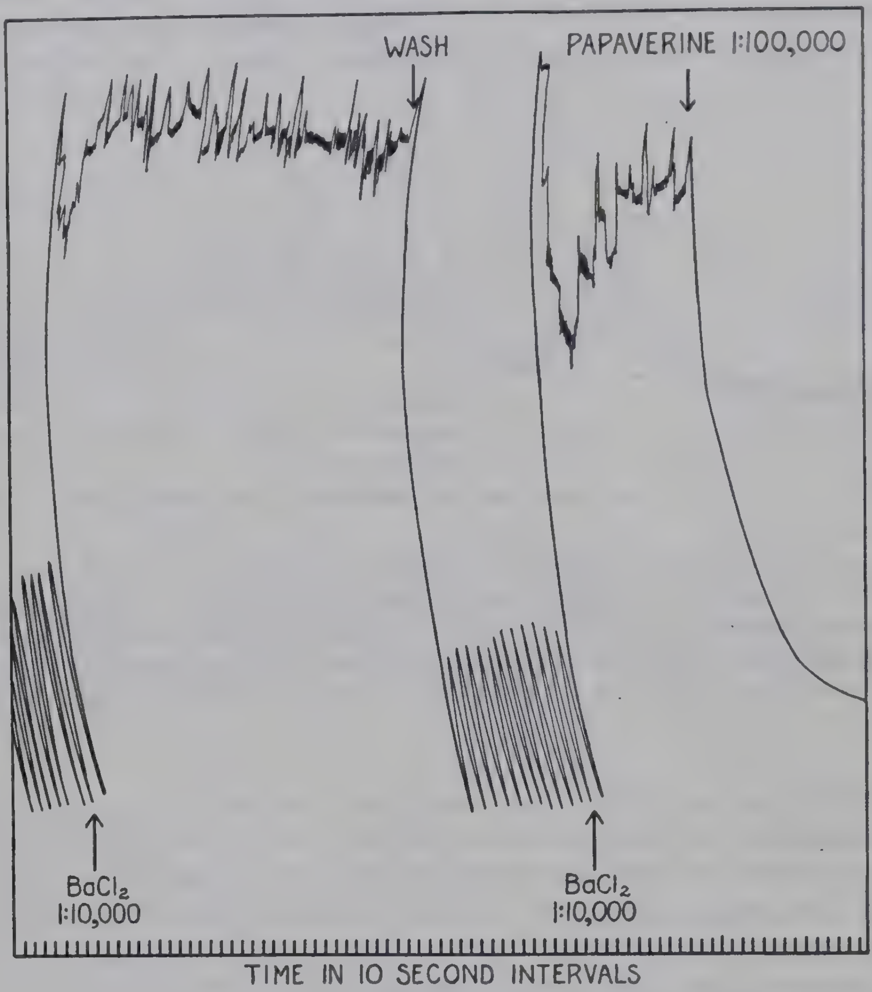


Figure 18. *The antispasmodic action of papaverine on the small intestine.*

Isolated strip of rabbit jejunum. Spasm produced by barium chloride (1:10,000) persists until the drug is washed from the organ bath. Papaverine hydrochloride (1:100,000) is capable of promptly counteracting the spasm produced by barium, and in addition normal peristalsis is temporarily suspended.

The nauseant and emetic actions of morphine and its derivatives have already been discussed. These responses are purely central in origin and result from a direct stimulation of the medullary emetic center.

Whereas the gastro-intestinal responses to opium and morphine are correctly viewed as unpleasant side-effects when these drugs are given for narcosis, yet these same actions at times become desirable therapeutic objectives in themselves. This is especially true in patients with gastro-intestinal hemorrhage, exhausting diarrhea or dysentery, peritonitis, etc.

Biliary Tract. Experiments performed on patients with T tubes in the common bile duct for drainage after exploratory operations show definitely that the hypodermic injection of 10 mgm of morphine sulfate causes a marked increase in biliary pressure (Walters and coworkers, 1937). The pressure rises from the normal of zero to 20 mm of water to a level of from 200 to 300 mm. This effect begins within five minutes after injection, reaches its peak in 15 minutes and persists for two hours or more. Symptoms often accompany the increased pressure and vary from epigastric distress to typical biliary colic. It is quite clear, therefore, that the relief afforded by morphine in biliary spasm is purely cerebral in origin. *Codeine* (60 mgm), pantopon (20 mgm) and *dilaudid* (two mgm) all cause a similar increase in intrabiliary pressure but the rise is neither as rapid nor as high as that after morphine.

Biliary spasm produced by morphine is evident roentgenographically as well as manometrically and a sharp constriction becomes apparent at the lower end of the common bile duct. This prevents emptying and thus causes the intraductal pressure to rise. Atropine (0.9 mgm subcutaneously) does not relax the morphine-induced spasm. Papaverine (32 mgm intravenously; 180 mgm intramuscularly) has no effect on the elevated biliary pressure caused by morphine. Inhalation of amyl nitrite is the most valuable agent for relaxing this type of biliary spasm (Figure 58). Nitroglycerin (0.6 mgm) administered sublingually also decreases the elevated intrabiliary spasm (Figure 59). The effect is less marked but more prolonged than that produced by amyl nitrite. Theophylline with ethylenediamine (0.24 gram) given intravenously is also quite effective (Figure 59). In Figure 19 is shown a record of the effects of morphine sulfate on biliary pressure.

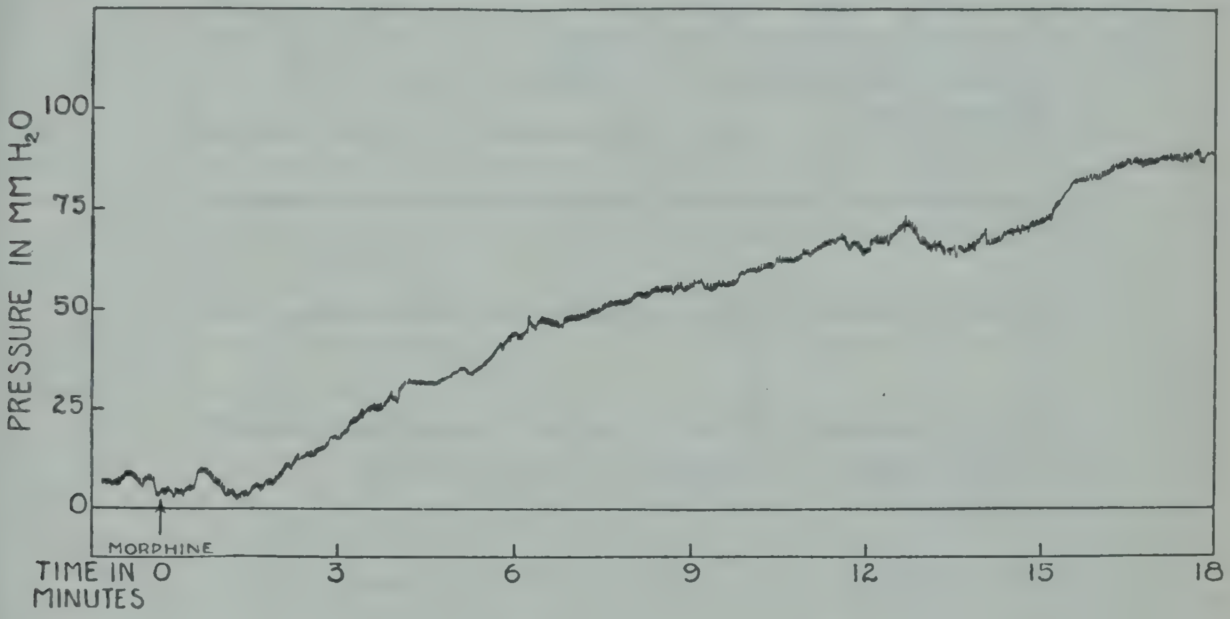


Figure 19. *The effect in man of the subcutaneous injection of 10 mgm of morphine sulfate on intrabiliary pressure.*

Kymographic tracing obtained by means of a water manometer connected to a T-tube inserted into the common bile duct for prolonged biliary drainage. Note the gradual rise in pressure which at times may reach a level of 300 mm of water. Dilaudid causes a similar rise. Typical biliary colic may occur. (After Butsch, McGowan and Walters, 1936. Courtesy of *Surgery, Gynecology and Obstetrics.*)

Ureter and Urinary Bladder. The intact human ureter responds to morphine by an increase in tone and amplitude of contraction. In more than a score of normal persons in whom ureteral activity was followed by hydrophorographic tracings and radioscopy, hypodermic injection of eight to 30 mgm of morphine caused the ureteral responses to appear within five minutes and to persist for at least three hours (Figure 20) (Ockerblad and collaborators, 1935). These clinical results confirm the experimental data obtained on animals. Papaverine and benzylisoquinoline drugs depress ureteral activity with respect to tone and rate and amplitude of contractions.

Atropine, although it has little effect on the ureter when given alone, can eliminate the morphine-induced ureteral spasm when given subcutaneously in a dose of 0.6 mgm. This is in sharp contrast to the inefficacy of atropine in relieving the gastro-intestinal and biliary spasm caused by morphine. The relief of renal colic by morphine is clearly due to central analgesia because the local action on the ureter would tend to aggravate the pain. These results also suggest that atropine should accompany morphine medication for ureteral colic, and that a mixture of opium alkaloids containing papaverine might offer greater relief than does morphine alone.

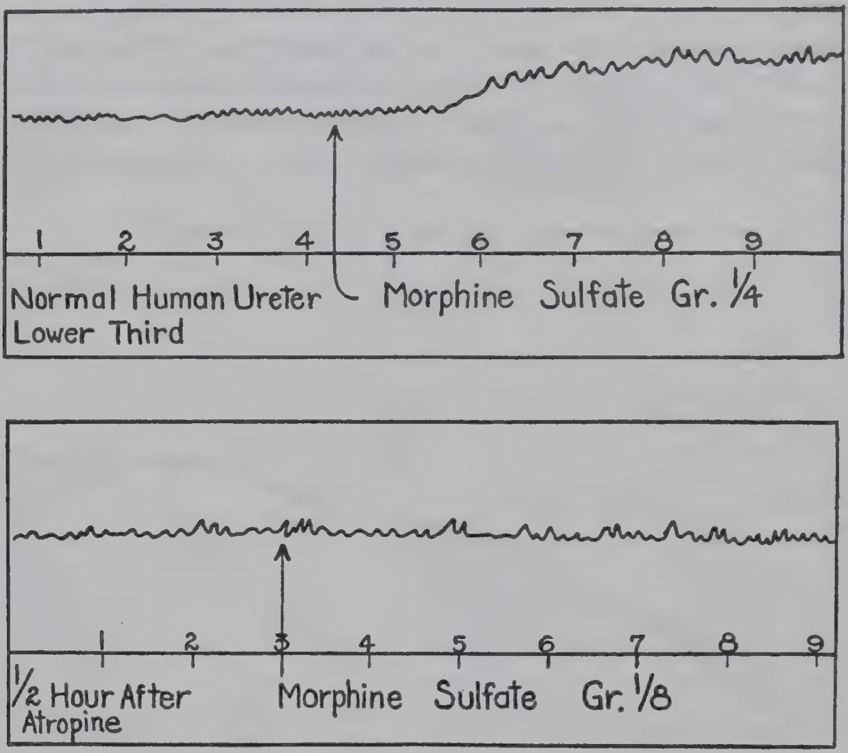


Figure 20. *The effects of morphine sulfate on the normal human ureter.*

Kymographic tracings obtained by means of a ureteral catheter and water tambour; time in minutes. The upper tracing shows the increase in ureteral tone and amplitude of contraction produced within two to three minutes by 15 mgm of morphine sulfate given subcutaneously. The responses may last longer than three hours. The lower tracing shows that the administration of 0.6 mgm of atropine sulfate prevents the ureteral response to morphine. (After Ockerblad, Carlson and Simon, 1935. Courtesy of the *Journal of Urology*.)

The tone of the detrusor muscle of the *urinary bladder* is augmented by morphine which therefore causes urinary urgency. The tone of the vesical sphincter is also enhanced by morphine which may thus make urination difficult. Furthermore, the patient is often inattentive to the stimuli arising from the bladder as a result of central depression, and catheterization therefore may be necessary. This is especially true in morphine poisoning.

Other Smooth Muscles. The *bronchial musculature* is stimulated to contract by morphine, but this effect is rarely if ever apparent from the use of therapeutic doses in man. Papaverine relaxes the bronchi. The *uterine muscle* is not directly affected by doses of morphine used in obstetrical analgesia. The alkaloid can influence the progress of labor in other ways, however, especially by preventing cooperation of the mother and depressing fetal respiration.

Cardiovascular System. Therapeutic amounts of morphine or its allied alkaloids have little if any effect on the blood pressure, heart rate or rhythm. Changes which occur are usually secondary to lessened physical activity or sleep. The vasomotor and vagal centers in man are unaffected by doses of morphine that readily cause respiratory depression. It requires toxic amounts of the alkaloid to produce central vasomotor depression, and the blood pressure falls only relatively late in the course of morphine intoxication. Even this fall is largely the result of asphyxia. This is evident from the fact that artificial respiration or administration of oxygen will cause the blood pressure to rise despite the persisting medullary depression. Anoxia results in capillary paralysis and if it is unrelieved shock follows. For this reason, the respiration and not the circulation receives most attention in cases of morphine poisoning.

Higher concentrations of morphine than can be attained clinically are required to affect the myocardium directly. The T waves in the electrocardiogram may occasionally be altered or inverted after large doses of morphine. The phenomenon may be due to respiratory depression causing relative anoxia of the myocardium. Errors may arise in the interpretation of the electrocardiogram of a patient suspected of acute coronary thrombosis if large amounts of morphine were recently administered to control pain.

Papaverine tends to relax the coronary vessels and in this manner may improve the circulation to the heart muscle. The actions of papaverine on blood vessels are discussed on page 208.

Skin. After therapeutic amounts of morphine in man, cutaneous blood vessels are relaxed. As a result, the skin of the blush area (face, neck, upper thorax) becomes flushed and hot. The mechanism of this vascular action is unknown but it appears to be a direct one on the blood vessels.

Sweating. Sweating is common after the administration of the opium alkaloids, especially morphine. Its cause is not apparent but may be related to an increased cutaneous blood flow. When Dover's powder is given as a diaphoretic, sweating is due in part to the opium content but more perhaps to the nausea caused by the ipecac.

Pruritus. Pruritus is not unusual after administration of the morphine alkaloids, and it is thought to be due to changes in cutaneous circulation. Both itching and sneezing are more apparent as the action of the opiate wears off. The nasal itching after morphine is the basis for the lay conception than an addict continuously scratches his nose. Allergic reactions are not uncommon and urticaria may be prominent. Marked anaphylactoid phenomena may result, especially from codeine administered intravenously.

Metabolic Effects. Morphine may cause a fall in *body temperature.* This occurs especially with large doses and is the result of lessened muscular activity, increased heat dissipation due to peripheral vasodilatation, and lessened sensitivity of the central mechanism for temperature regulation. With therapeutic doses of morphine, the depression of body temperature is not significant. The *metabolic rate* in man may be lowered slightly within the first hour after hypodermic injection of 10 to 20 mgm of morphine. This effect is secondary to a decrease in muscular tone as a result of central depression. The *hyperglycemia* noted after morphine in animals is inconstant, and the effect of the alkaloid on blood sugar in man is clinically unimportant. The rise in blood sugar is in some way related to the release of sympathin for only by complete sympathectomy can one completely abolish the hyperglycemia (Bodo and associates, 1938). The metabolic changes from overdoses of morphine such as marked hyperglycemia, glycosuria, increase in blood lactic acid, decrease in carbon dioxide combining power of the blood, etc., are caused by the anoxia resulting from the depression of respiration.

Local Actions. It has been stated that the opium alkaloids have no local anesthetic action and that their local use for analgesia is thus irrational. Indeed, the phenanthrene alkaloids are quite irritant to the mucosa and abraded skin. This is particularly true of *dionine*. The reactive mucosal hyperemia which this chemical produces when applied locally is employed in the treatment of indolent corneal ulcers, uveal exudates and vitreous opacities. A few drops of a solution of dionine hydrochloride (two to 10 per cent) are instilled into the conjunctival sac to cause vascular dilatation and therapeutic hyperemia. The drug may also be incorporated in an ophthalmic ointment (10 per cent) or a little of the dry powder itself may be placed in the eye.

Absorption, Fate and Excretion of the Opium Alkaloids. *Absorption.* The opium alkaloids are readily absorbed from the gastro-intestinal tract. The intact skin is not permeable to morphine but the scarified epithelium allows some of the drug to enter the circulation. The differences in time necessary for the hypodermically injected morphine alkaloids to manifest their actions are due to variations in rates of absorption from the subcutaneous tissues. When the drugs are given intravenously, they all act after the same interval of time.

Fate. Morphine is partly excreted from the body but mainly destroyed in the tissues. In man, 90 per cent is detoxified, especially by the liver. Temporary storage of morphine prior to destruction occurs mainly in the liver and skeletal muscles. Detoxification proceeds slowly. Only one-half of the total amount is destroyed in the first 24 hours. Inasmuch as the narcotic effects of a single dose are usually over within four hours, it is clear that some change must occur in the morphine prior to its destruction in the body.

Excretion. Excretion is almost entirely by way of the urine. In man, about one-tenth of the ingested drug is excreted in the urine and this occurs within the first four hours. A small fraction is eliminated in the feces even when morphine is given parenterally. The inconsequential amount excreted in the gastric juice does not warrant the dangerous procedure of continuous gastric lavage in morphine poisoning. Small amounts of morphine may be excreted in the milk when large doses are taken. This may at times be of importance because suckling infants are quite sensitive to the drug and addiction of nurslings has been reported. Traces of the alkaloid may appear in the saliva, sweat and other secretions. Morphine readily crosses the placental barrier and enters the tissues of the fetus. Indeed, the newborn child may show withdrawal symptoms if *in utero* it has been repeatedly exposed to morphine.

Codeine, in contrast to morphine, is largely excreted in the urine. About 80 per cent of the codeine administered can be accounted for in this way. Papaverine is not recoverable in the urine, feces or tissues, and its fate in the body is unknown. It is probably destroyed.

Tolerance. A characteristic feature of the phenanthrene alkaloids of opium is the tolerance to them which develops as a result of their repeated use. Tolerance does not occur uniformly to all the manifestations of morphine action. The depressant effects on the nervous system, such as respiratory depression, analgesia and stupefaction, fail to appear after continued employment of the drug unless the dose is increased. Tolerance does not occur to the excitatory responses elicited by the opium alkaloids. Thus codeine or heroine addicts experience stimulation. Also the effects on the bowel and pupillo-constriction continue and the morphine habitué manifests miosis and suffers from constipation alternating with diarrhea.

Cross-tolerance exists between the various phenanthrene alkaloids, and the person tolerant to morphine is also tolerant to dilaudid, codeine and heroine. Experimentally it has been shown that there is also a cross-tolerance between the emetic effects of morphine and apomorphine.

Different individuals require varying periods of time before the repeated administration of morphine results in tolerance. As a rule, however, after about two weeks of continued use of the same dose of alkaloid the usual depressant effects fail to appear. This time interval, however, may vary widely in either direction. When medication ceases, tolerance usually disappears within a few days to two weeks, and small doses will again produce characteristic depression. If the use of the drug is resumed, however, tolerance develops more rapidly than it did initially.

Large doses may eventually be taken by the tolerant person. The addict, for example, may ultimately use daily 20 to 200 times the ordinary therapeutic dose of opiate. Tolerance is never absolute, however, and a dose exists which is capable of producing death from respiratory depression even in the addict. Overdosage of opiate through error or from the misjudging of the degree of tolerance is a common cause of fatality among addicts. On the other hand, the tolerant person can receive much larger doses than he is accustomed to without any evidence of untoward results. Thus, Light and Torrance (1929) injected 30 grains of morphine intravenously in an addict within two and one-half hours, and no change occurred in pulse, respiration, blood pressure or other vital signs. The usual dose for this individual was only four grains. Again, the tolerance of the addict for morphine can be increased within three to five days from one gram daily to four grams daily without causing any detectable physiological changes.

The *mechanism of tolerance* to morphine is unknown. Various theories have been proposed but none of these satisfies all features of the phenomenon or survives rigorous examination. There is no evidence that the tolerant person excretes the drug more readily. Decreased absorption cannot be the explanation because large doses are tolerated when given intravenously. It has been claimed that tolerance is due to an ability of the body to destroy morphine more rapidly than normal. Many experimental data oppose this view. As stated, addicts tolerant to large oral doses are also tolerant to the same dose given by vein, a route which allows the full concentration of morphine rapidly to reach the brain cells before the mechanism of detoxification can effectively begin to operate. Furthermore, it is difficult to explain the persistent sensitivity to small amounts of morphine of certain brain centers and the intestine of the tolerant person if the alkaloid is destroyed more rapidly. Interesting clinical data on the fate of morphine have been obtained by Light and coworkers (1929–1930). They found that, regardless of the dose administered, addicted individuals, in a manner similar to that of normal persons, always excrete about 10 per cent of the morphine within four hours. The remaining 90 per cent rapidly undergoes a chemical change in the tissues and is no longer recoverable as morphine. Evidence for this exists in the fact that, after abrupt withdrawal, only 10 per cent of the last dose taken can be recovered in the urine. Withdrawal symptoms and craving appear as soon as this fraction is excreted, that is, after four hours. Similar results have also been obtained by other workers in normal and addicted dogs, all of which excrete the same percentage of the amount administered regardless of the size of the dose. Thus the rates of destruction and elimination of morphine are more closely related to the dose taken than to the extent or duration of addiction.

There is some evidence that tolerant animals may store more morphine in skeletal muscles than do the non-tolerant, but this requires further confirmation. The postulate of an "antimorphine" immune substance in tolerant patients has received no experimental support. Indeed, the evidence is strongly against the existence of such a substance. The most acceptable theory is that tolerance to morphine is a cellular phenomenon, that is, certain cells of the brain acquire the ability to function normally despite the presence of concentrations of morphine which ordinarily would depress their activity. In this respect, cellular tolerance to morphine resembles that to alcohol.

Idiosyncrasy and Variations in Response. Idiosyncrasy to the opium alkaloids manifests itself in many ways. *Nausea and vomiting* after morphine are fairly frequent in some patients, especially women. The basis for this excitation has already been discussed. When morphine is indicated in a patient known to respond to it with vomiting, the emesis can often be circumvented by giving a small preliminary dose of the drug which barely stimulates the emetic center. This is followed in 15 to 30 minutes with the remaining larger fraction of the full therapeutic dose which begins to take effect at a time when the vomiting mechanism has passed its stimulatory phase and is depressed. Other excitatory phenomena occurring after the administration of opium alkaloids are *tremors,* rarely *delirium,* more rarely convulsions, and sometimes *insomnia* as a late sequel. Hypersensitivity to pain after analgesia has worn off is nearly always noted. This hyperalgesia occurs after the administration of other drugs which relieve pain and can hardly be classed as an idiosyncrasy.

Allergic phenomena are not unknown after the administration of morphine and its derivatives. Urticaria and skin rashes occur, and contact dermatitis has been reported in nurses and pharmaceutical workers (Jordan and Osborne, 1939). Pruritus and sneezing have already been mentioned. Codeine is apt to cause wheals at the sight of injection, and marked anaphylactoid reactions have been reported to occur after the intravenous use of this drug. In some patients, codeine causes rather severe epigastric pain.

Infants are especially susceptible to the central depressant actions of morphine. The sensitivity is particularly noted before weaning, during which time great care must always be observed in using any preparation containing morphine. One drop of laudanum is reported to have caused alarming symtoms. Children, in contrast, are more tolerant of morphine (per pound of body weight) than are adults. *Old and debilitated patients* are more sensitive to the depressant actions of morphine and the dose should therefore be reduced.

The patient's illness and the state of the reflex excitability of the nervous system also condition the response to morphine. Thus individuals with *cerebral edema, cardiac psychoses* or *fever* may be excited by the drug. Persons with *myxedema* often react with marked narcosis to small doses of morphine, and this alkaloid must be prescribed with caution when the metabolic rate is low. Hyperthyroid patients, in contrast, usually tolerate morphine very well. Individuals suffering from *severe pain* can withstand large amounts of morphine without manifesting subjective or respiratory depression. For example, the person with pain from acute coronary thrombosis may receive with safety three or even four times the usual therapeutic dose of morphine before relief is obtained. There appears to be little basis for the belief that morphine is contraindicated in chronic nephritis, and the alkaloid may afford considerable symptomatic benefit in uremia.

Patients with *pruritus* may suffer an exacerabation of itching due to the administration of opiates. When *increased intracranial pressure* exists, care is required in the use of morphine due to the increased likelihood of depression of respiration. Morphine also tends to elevate the intracranial pressure (Kennedy and Wortis, 1931). In a person with an *hypertrophied prostate* or *ureteral stricture,* the use of morphine may precipitate acute urinary retention requiring repeated catheterization. The use of morphine in *bronchial asthma* is often dangerous and has caused death.

Preparations, Doses and Routes of Administration of Opium and Its Alkaloids. *Powdered Opium,* U.S.P., B.P. (Meconium, Thebaicum). The source, chemistry and alkaloidal composition of opium have already been given. Powdered opium is a brown, bitter, granular powder supplied for clinical use in capsule, tablet or pill form. The average adult dose is 0.06 gram taken orally. This is equivalent to six mgm of morphine because the official morphine content of opium is 10 per cent by weight. Formerly opium had a peculiar and characteristic odor detectable in the excretions of the patient, but the official tincture is now deodorized.

Opium is also available in the form of *Gum Opium* (U.S.P.) and *Granulated Opium* (U.S.P.) The dose of either is the same as for the powder. The N.F. contains an *Extract of Opium,* one gram of which represents two grams of opium and the dose of which is 0.03 gram. The B.P. contains an identical preparation, *Dry Extract of Opium. Aromatic Powder of Chalk with Opium,* B.P., contains 2.5 per cent of powdered opium. The dose is 0.6 to 4.0 grams (equivalent to 1.5 to 10 mgm of morphine). The above preparations are infrequently employed.

Tincture of Opium, U.S.P., B.P. (Laudanum; Tincture of Deodorized Opium). This tincture is a hydro-alcoholic solution containing 10 per cent of opium (one per cent of morphine). The average adult dose is 0.3 to 2.0 cc, taken orally.

Camphorated Tincture of Opium, U.S.P., B.P. (Paregoric). This tincture contains 0.4 per cent of opium (B.P., 0.5 per cent), or 0.04 per cent morphine. Also included are benzoic acid, camphor and oil of anise. The average adult dose is four cc which corresponds to 16 mgm of opium or 1.6 mgm of morphine. Paregoric by tradition is used especially for children, but represents a needlessly complex therapeutic survival of a former day.

Powder of Ipecac and Opium, U.S.P., B.P. (Dover's Powder). This contains 10 per cent each of ipecac and opium, and consists of a white or very light brown powder. The average adult dose is 0.3 to 0.6 gram, the equivalent of three to six mgm of morphine, respectively. The powder has been employed especially as a diaphoretic, and the mechanism involved has been discussed. The drug is no longer extensively used.

Ipecac and opium are also available together in *Tincture of Ipecac and Opium* (Tincture of Dover's Powder), N.F., dose 0.5 cc, and *Syrup of Ipecac and Opium* (Syrup of Dover's Powder), N.F., dose 4.0 cc.

Compound Mixture of Opium and Glycyrrhiza, U.S.P. This drug, known as "Brown Mixture," is another therapeutic relic. It contains 12 per cent of paregoric, some tartar emetic and a little sweet spirit of niter. It is needlessly complex and little used today. The average adult dose is four cc, taken orally.

Morphine. The alkaloids of opium, especially morphine and codeine, are employed much more extensively than the galenical preparations. Morphine is available as the alkaloidal base, but is usually prescribed in the form of its water-soluble salts. The two most common preparations are *Morphine Sulfate,* U.S.P. and *Morphine Hydrochloride,* N.F., B.P. The B.P. also includes *Morphine Tartrate.* These salts are bitter white powders, quite soluble in water and possess characteristic alkaloidal incompatibilities. Solutions of morphine salts are not irritating on injection.

Salts of morphine are also available in two official solutions. *Solution of Morphine Hydrochloride,* B.P., is an unflavored hydro-alcoholic solution containing one per cent of the alkaloidal salt. The dose is 0.3 to 2.0 cc (three to 20 mgm of morphine). *Compound Syrup of White Pine with Morphine,* N.F., contains only 0.04 per cent of morphine sulfate in compound syrup of white pine. The dose is four cc (1.6 mgm of morphine) or more.

The average oral adult dose of a morphine salt is eight to 20 mgm, but the amount varies with the patient's illness, factors of idiosyncrasy and the level of reflex excitability of the nervous system. The hypodermic dose is somewhat smaller. Occasionally a salt of morphine (2.5 to 15 mgm) may be given intravenously, as in emergencies when analgesia is needed quickly or when the regular preoperative dose of opiate has been forgotten or cannot be given soon enough (Betlach, 1937). The analgesic effects start immediately and reach their peak in 20 minutes.

The dose of opiates for children is best learned as such and modified to suit the particular case. In general, however, for infants over 10 months of age, the dose may be calculated on the basis of weight in pounds ($\frac{\text{wt}}{150} \times$ adult dose). For infants under 10 months of age, this dose should be halved ($\frac{\text{wt}}{300} \times$ adult dose).

Codeine, U.S.P., B.P. Codeine is available as the free alkaloidal base and in the form of its water-soluble salts. The most common salts of codeine are *Codeine Sulfate,* U.S.P., and *Codeine Phosphate,* U.S.P., B.P. The latter has the advantage of being much more soluble in water (1:2.3 as compared to 1:30). The average dose for adults is 16 to 60 mgm, given orally or hypodermically. Smaller amounts may be used when repeated medication is required.

Codeine is methylmorphine and the chemical basis for its pharmacodynamic differences from morphine has been presented. Codeine may be viewed as a weakened morphine which fails to cause proportionately greater narcotic effects as the dose is increased. Indeed, large amounts of codeine cause excitement, not depression. The analgesic potency of codeine is less than one-sixth that of morphine. If 60 mgm of codeine fail to relieve pain, larger doses rarely succeed (page 196) and are likely to cause restlessness and excitement. Codeine is only one-fourth as potent as morphine in its ability to cause subjective and respiratory depression. For example, the sleep induced by codeine is not as sound or refreshing as that from morphine, and serious respiratory depression is practically unknown even from large therapeutic amounts of the alkaloid. Death directly ascribable to codeine is practically unknown and the lethal dose for man cannot be stated. Nausea, vomiting, constipation and miosis are all less prominent after a given amount of codeine than after one-quarter this amount of morphine. Codeine is excreted to the extent of 80 per cent in the urine and is thus handled by the body in a manner considerably different from that for morphine.

Both tolerance and addiction occur to codeine. Withdrawal symptoms may not necessarily be less severe than in morphine withdrawal (Table 11; page 217). Codeine is rarely used by drug habitués, unless as an adulterant, because it does not produce the desirable degree of euphoria in the potential addict. The large doses required make trafficking in it difficult. When codeine is substituted in morphine addicts, five times as much may be needed to replace morphine and prevent symptoms of withdrawal. It must be reemphasized that codeine is an addictive drug, and the opinion current in some quarters that the alkaloid is benign in this respect is entirely without foundation (Himmelsbach, 1934).

Heroine (Heroin). Heroine is no longer an official drug in the U.S.P., but is included in the B.P. (*Diamorphine Hydrochloride*). Its importation and manufacture in the United States are prohibited by law, although the present available supply may be legally dispensed. The usual salt prescribed is the hydrochloride. The chemistry of heroine has already been presented. The dose of heroine is one-fourth that of morphine, that is, two to five mgm. Heroine is one of the most analgesic of the morphine derivatives, being from four to eight times as potent as morphine in this respect. It is also four or more times as depressant to the respiration. When given hypodermically, its analgesic action comes on more quickly than is the case with the other opiates. Heroine is excreted unchanged almost entirely by the kidney. It is said that in the addict the alkaloid is no longer recoverable in the urine. This requires confirmation.

The danger of heroine lies in the ease with which addiction to it occurs, due to the intense euphoria which often supplants subjective depression, and the absence of unpleasant side-actions such as vomiting and constipation. The type of addiction which heroine produces is of a serious nature. The heroine addict is difficult to treat, usually relapses after apparent cure and often represents a dangerous, asocial and criminal type of personality. He not only experiences euphoria but this is intermingled with excitation. Whereas the morphine addict takes his daily requirement of morphine in order to keep normal and prevent the appearance of withdrawal symptoms, the heroine habitué continues his drug rather for the euphoric excitation it affords. Considering its dangers, heroine has no indispensable advantages over morphine.

Dilaudid, N.N.R. This derivative of morphine, first described in 1923, is *dihydromorphinone hydrochloride.* It is a fine, white, odorless, crystalline, water-soluble salt, the chemistry of which has been given. The average adult dose of dilaudid is one-fourth or less than that of morphine, namely, two to four mgm. This may be given orally, hypodermically or by suppository. The duration of analgesic action of dilaudid is definitely shorter than that of morphine. Slower absorption and hence longer action can be obtained by the use of rectal suppositories. If given at bedtime, a night's relief from pain may often be obtained in this manner.

Dilaudid is about ten times more analgesic than morphine but only about four times more somnifacient. This allows dilaudid to be used for relief of pain with a minimal hypnotic effect, and sleep need not occur in order to obtain analgesia. The margin of safety of dilaudid is no greater than that of morphine. Side-actions from dilaudid, such as nausea, vomiting, and constipation, are apparently less marked than from morphine. Euphoria is also less evident after dilaudid than after morphine.

Both addiction and tolerance occur to dilaudid. Although some (but not all) animal experiments indicate that the drug is somewhat less likely to cause addiction than is morphine, clinical evidence on this point does not support such a conclusion. Cases of addiction to dilaudid have been reported; thus it is essential to use the alkaloid with the same precautions which are employed for morphine. In fact, the shorter analgesic action of dilaudid and the consequent necessity to step up the injection rhythm when the drug is used for the relief of chronic continuous pain favor the more rapid development of dependence on dilaudid as compared with morphine (King and associates, 1935; Daland, 1936). The phenomena seen after substituting dilaudid for morphine in addicts and then withdrawing the substituted drug are clearly depicted in Table 11. The Federal Narcotic Regulations naturally apply to the use and sale of dilaudid.

Dionine. Dionine is available as *Ethylmorphine Hydrochloride,* U.S.P. It is a synthetic derivative consisting of a white or faintly yellow, odorless powder which is quite soluble in water. Dionine may be viewed for therapeutic purposes as having the same pharmacological properties as codeine. Dionine, by tradition perhaps, is rarely employed for its systemic effects but is used only in the eye for the local irritation it produces.

Thebaine. This natural alkaloid of opium is not used clinically. It is a convulsant poison which produces strychnine-like stimulation rather than narcosis.

Pantopon. Pantopon, also called *omnopon* and *pantopium hydrochloride,* is a mixture of the purified opium alkaloids in the proportions occurring naturally. Thus it is a purified opium and is devoid of inert material. Pantopon has four times the morphine content of opium and by weight is close to 50 per cent morphine. The usual therapeutic dose is 20 mgm. It is available for oral use and for parenteral injection. Pantopon has the obvious advantage that it can be injected whereas opium preparations cannot.

The claims made for pantopon, that it produces fewer side-actions and allows the benefits of the central action of morphine and the peripheral antispasmodic effect of papaverine, are not substantiated. The papaverine content of pantopon is so small that it cannot contribute much to the total response. Clinical evidence indicates that the analgesic potency of pantopon is not materially greater than would be expected on the basis of its morphine content (Hayman and Fox, 1937; Wolff and coworkers, 1940).

Papaverine Hydrochloride, N.F. Papaverine is the most important member of the benzylisoquinoline group of opium alkaloids. It is marketed as the water-soluble (1:40) hydrochloride salt which consists of a white, crystalline, odorless and slightly bitter powder. The average adult dose is 30 to 80 mgm orally or intramuscularly, and 10 to 60 mgm intravenously. The toxicity of papaverine is very low and the ingestion of more than ten times the therapeutic dose has not resulted in untoward effects. Because it is contained in opium, papaverine comes under the Federal Narcotic Regulations despite the fact that it is devoid of narcotic action.

The pharmacological properties of papaverine have already been contrasted with those of morphine and may be summarized here. The actions of papaverine on the central nervous system are negligible and the drug causes neither sleep nor analgesia in therapeutic doses. Large amounts may actually increase reflex excitability. Papaverine relaxes many smooth muscles of the body, especially those of blood vessels. This relaxation occurs particularly if spasm exists. In those smooth muscles exhibiting phasic activity, tone is decreased and the amplitude and frequency of contraction are lessened. The drug does not paralyze the muscle cell which still responds to drugs and stimuli causing contraction. The muscles responding to the alkaloid are those of the bronchi, gastro-intestinal tract, ureters, biliary system and blood vessels, including the coronary arteries. Essex and associates (1940), for example, studied the effect of papaverine on the coronary circulation in trained unanesthetized dogs by means of thermostromuhr units placed on the coronary arteries. They found that the drug markedly enhanced coronary blood flow when given intravenously in doses comparable to those employed clinically, a finding in agreement with the observations of Anrep on the human heart-lung preparation.

The antispasmodic action of papaverine, however, is not clinically useful in all instances. Papaverine is not nearly as effective as epinephrine in bronchial asthma. Its value in the therapy of angina pectoris is also equivocal. Papaverine does not appear to relax the spasm induced by morphine in the human biliary ducts. Thus, the drug lacks the general usefulness of the nitrites as an antispasmodic.

The best therapeutic results have been obtained with papaverine in patients with peripheral or pulmonary arterial embolism. Papaverine given intravenously has prevented amputation of limbs and preserved life. The drug acts not on the obstructed vessel but by increasing collateral circulation in reflexly constricted vascular beds. Symptoms such as pain, paresthesia and paresis may be completely relieved and adequate circulation restored within a few minutes after the intravenous injection of 20 to 100 mgm of papaverine hydrochloride. The drug is a useful medical adjunct to embolectomy or therapy by passive vascular exercise. The peripheral vasodilatation produced by papaverine has also proved of value in cases of threatened gangrene, as from ergotamine, and it may be of service in certain other forms of peripheral vascular disease.

In *Raynaud's disease,* Mulinos and associates (1939) have obtained promising results from the use of papaverine hydrochloride (60 to 120 mgm) administered intravenously in conjunction with histamine iontophoresis. Littauer and Wright (1939) report that papaverine hydrochloride (30 mgm) given intravenously was uncertain in action and generally ineffective in producing vasodilatation in patients with *thromboangiitis obliterans* or *arteriosclerosis obliterans.*

In *pulmonary embolism,* papaverine may be injected intravenously in the dose of 30 mgm or more. One mgm of atropine may be administered simultaneously by the same route. In a review of a number of cases of pulmonary embolism treated with papaverine, Takats and Jesser (1940) point out that 18 of 22 patients survived (82 per cent) as compared with a control group of 100 cases in which there were only 13 survivals (13 per cent). These figures, although not conclusive, are quite impressive.

Narcotine. This chemical is another opium alkaloid of the benzylisoquinoline group. Despite its name, narcotine is not narcotic and, in general, resembles papaverine in its pharmacological actions. Narcotine has no therapeutic uses.

Narceine. This alkaloid occurs in opium and belongs to the papaverine group. It lacks specific pharmacological properties, probably because of its insolubility and the consequent lack of absorption. It has no clinical uses.

Acute Morphine Poisoning

Acute morphine poisoning usually results from attempts at self-destruction or from clinical overdosage. It is difficult to state the exact dose of morphine which is toxic. The susceptibility to morphine of infants, the aged and myxedematous individuals has been mentioned. Others are quite tolerant to large doses, especially those suffering severe pain. The addict, of course, can withstand much larger doses than he usually takes. As a rule, however, the toxic dose of the alkaloid for a normal adult who is not in pain is about 60 mgm. Serious symptoms nearly always follow the ingestion of 100 mgm of the drug, and the outlook becomes progressively less hopeful as amounts greater than this are taken. Doses of 250 mgm usually cause death.

In fatal cases, death occurs in about six to 12 hours after the drug is taken, although it may result within the first hour. The longer the patient survives the better are his chances for recovery, because destruction and excretion of the poison are taking place and effective therapeutic measures may be instituted. The postmortem findings are purely those of asphyxia. Morphine can be recovered from the urine, tissues and excreta and can be identified pharmacologically and chemically. These are important considerations for medico-legal cases.

Symptoms. By the time he is seen by the doctor, the patient who has ingested an overdose of morphine is usually asleep or stuporous. If a large dose has been taken, ordinarily he cannot be aroused and soon sinks into a *profound coma.* The breathing is quite slow and only two to four respirations may occur per minute. Cheyne-Stokes breathing may be noted. The patient is *cyanotic* and the skin of the face shows a mottled purple flush. The *blood pressure* at first is maintained near normal because morphine has little direct effect on the vascomotor center or the cardiovascular system. As the respiratory exchange becomes poorer, however, the blood pressure falls progressively until it reaches shock levels. If adequate oxygenation is restored early, the blood pressure will again rise; but if anoxia persists untreated for any length of time, the capillaries are damaged and *shock* supervenes. More fundamental measures are then necessary to elevate the blood pressure. The cardiovascular abnormalities in morphine poisoning are thus almost entirely secondary to the respiratory depression which should therefore be the focal point of therapy.

The *pupils* are symmetrical and pinpoint in size in acute morphine intoxication. As asphyxia intervenes, they may dilate markedly. Overdoses of chloral hydrate and barbiturates can also cause miosis but it is not as constant or as pronounced as after morphine. *Urine formation* is considerably depressed and urine flow may cease secondary to the low blood pressure. The *body temperature* falls and the skin becomes cold and clammy. The *skeletal muscles* are flaccid, the jaw relaxed and the tongue may fall back to block the pharyngeal airway. The *Babinski great toe sign* is often positive and, if not, it may become so during periods of apnea. Occasionally *skin rashes* and urticaria develop, and if the stupor is not great reflex scratching of the skin and nose due to pruritus may be prominent. Atypical features of excitation may occur in morphine intoxication prior to the depression. These include restlessness, delirium and vomiting. When death occurs, it is due to *respiratory failure* and the heart beats feebly for a short interval after breathing ceases. Death may also be due to shock or *pulmonary complications,* especially pulmonary edema or pneumonia.

Diagnosis. The triad of coma, pinpoint pupils and greatly depressed respiration strongly suggests morphine poisoning. Other central depressants such as alcohol, chloral hydrate and barbiturates may simulate this intoxication. In few other conditions, however, are the respirations so characteristically depressed, the pupils quite so small, or the coma so rapid in onset and progressive in development as in morphine poisoning. The history is helpful, if obtainable, and at times chemical examination of the suspected material or of the urine and gastric contents may be necessary to establish the diagnosis beyond question.

Treatment. Therapy follows the same general plan as for barbiturate intoxication, but attention is focused especially on the respiration. Prompt diagnosis and effective therapy are needed to save life. If the patient can be kept alive for 12 hours or longer, the prognosis improves. However the danger of late pulmonary complications is ever present.

Lavage of the stomach should be instituted if the poison was taken orally, and this should be done even if the patient is not seen until late. Some morphine may still be in the stomach and the stimulation incident to the passage of the gastric tube is not undesirable. The lavage water should be either a 1:2000 solution of potassium permanganate or it should contain one cc of tincture of iodine. Emetics should not be used because they are rarely successful and may add to the morphine depression. The practice of continuous or repeated gastric lavage should be abandoned. Little if any morphine is excreted into the stomach and the patient may be seriously depleted of electrolytes by such therapy. Magnesium sulfate, 30 grams in solution, should be administered before the stomach tube is removed in order to expedite the passage of unabsorbed poison through the bowel.

Stimulation of the respiration is accomplished by the use of caffeine with sodium benzoate, 0.5 gram given parenterally, or by enemas of strong black coffee. Theophylline with ethylenediamine may also be used as a medullary respiratory stimulant and is given in doses of 0.5 gram intramuscularly or intravenously. The xanthines may be repeated at intervals as needed. Ephedrine sulfate, 20 to 40 mgm intramuscularly, is not only a medullary stimulant but also raises the blood pressure and acts centrally to lessen narcosis. It may be repeated hourly if necessary. Inhalation of carbon dioxide (10 per cent) in oxygen is a potent measure for stimulation of breathing. Coramine, metrazol and atropine may also be used. The latter should be given only once and in a dose not to exceed 1.5 mgm. Oxygen therapy may be continued for hours if necessary. Reflex respiratory stimulation such as that caused by inhalation of ammonia or injection of camphor is usually valueless in the severer grades of morphine poisoning. If breathing has almost ceased, artificial respiration should be resorted to without delay and continued until an adequate stream of oxygen can be fed by catheter directly into the trachea. If the heart is functioning and oxygen is being delivered to the lungs, the patient will not readily die. This simple fact is lost sight of too often in the emergency treatment of the patient *in extremis.*

The blood pressure, if low, can often be elevated merely by improving the oxygenation of the patient's blood; this is the reason that attention to the respiratory exchange is so important. Several of the drugs used to stimulate respiration, especially ephedrine, may also raise the blood pressure. If the blood pressure is low due to shock from protracted capillary anoxia, a shock regimen must be followed as outlined elsewhere.

The degree of narcosis should be lessened if possible. Ephedrine and caffeine assist in this objective. If stupor has not yet occurred, every attempt should be made to keep the patient awake and he should be kept moving if possible. Strychnine and picrotoxin are not employed because morphine itself is a stimulant of the spinal cord. Diuresis has not been proved of value in promoting recovery from morphine poisoning, but copious amounts of fluid may be given empirically to insure against dehydration and acidosis. Furthermore, the kidneys should be kept functioning because they represent the chief channel for excretion of that morphine which escapes destruction in the body. Hypertonic solution of glucose given intravenously is a good diuretic agent, and also provides readily utilizable food and assists in maintaining blood volume if shock is impending.

Additional measures consist of maintenance of body temperature, frequent changes in the patient's posture to forestall development of hypostatic pneumonia, and prevention of aspiration during gastric lavage. Prolonged coma requires that attention be given to the intake of food, fluids and electrolytes and to distention of the urinary bladder. A long period of sleep usually precedes full return to consciousness. After recovery, the severe obstipation can be treated by enemas and laxatives. The itching, headache, nausea, vomiting and confusion during the recovery period may require symptomatic therapy.

Acute poisoning by heroine or dilaudid is treated in the same manner as poisoning by morphine. Codeine rarely causes fatalities because overdoses may stimulate rather than depress, and the chances for recovery are better. Poisoning by papaverine has not been reported.

Opium Addiction: Chronic Morphinism

The narcotic alkaloids of opium head the list of drugs to which addiction occurs, and this fact is a major consideration in their therapeutic use. The opium habit has existed for centuries in the Orient where the drug is habitually smoked by millions of people. In the United States and Europe, the pure alkaloids are used, and the addiction takes a more serious form.

Etiology. The etiology of narcotic addiction varies but the habitué himself cannot be believed regarding the origin of his habit. It is likely that only a small percentage becomes addicted as a result of the therapeutic use of opiates. The vast majority of narcotic habitués are constitutional psychopathic inferiors, and the habit is only one manifestation of their fundamental personality defect. In this sense, they do not differ from chronic alcoholic addicts. The use of an opiate provides an escape mechanism from reality, a way of release from the failures and disappointments of everyday life, a means of bridging the gap between ambition and accomplishment. Some of these individuals start the habit as a result of evil associates, of curiosity or as a means of dissipation. When a "thrill" or "kick" is desired, according to the language of the addict, the dose must be increased as tolerance develops in order to duplicate the original dreamy state of euphoria. Most cocaine and heroine addicts are in this category. On the other hand, the few persons who acquire the habit accidentally from the therapeutic use of a narcotic increase their dose as little as possible and continue to take the drug only to prevent unpleasant withdrawal symptoms.

Incidence. The exact incidence of narcotic addiction in the United States has been a subject of considerable discussion and inquiry (*see* Terry and Pellens, 1928). Estimates as high as one million have been offered but this figure is considered much too large by many authorities. The number of addicts is probably not over 30,000 (about two in 10,000) at the present time (Report by the Government, 1939).

Types of Drug Used. The narcotics used in the United States are particularly heroine, morphine and cocaine,* in the order named. Heroine has greater powers of addiction than other drugs, produces greater euphoria and "stimulation," requires smaller doses and is easier to traffic in illicitly. The addiction it causes is dangerous and difficult to cure. Probably 75 per cent of addicts in the Eastern seaboard area use heroine. Codeine addiction is rare because the drug produces practically no euphoria and possesses relatively weak addicting power. The few codeine addicts that are found are usually patients who originally received the drug for clinical purposes.

Every conceivable method and route is used to get the narcotic into the body. Morphine and heroine, however, are ordinarily taken hypodermically and occasionally intravenously; cocaine and also heroine are employed by snuffing. The use of opium preparations is rare in the United States. Occasionally, however, a paregoric addict is discovered. The daily dose of this mixture may reach a quart a day.

Time Required for Addiction. Addiction occurs after varying periods of time. While it usually requires more than two weeks, it may occur in a few days and in some unstable personalities after only a few doses. Great care should therefore be exercised not to prescribe narcotics for a longer period of time than is absolutely necessary. The continuous employment of opiates to relieve the pain of terminal diseases or neoplastic growths does not come under the scope of the present discussion and addiction under such circumstances is unavoidable.

Amount of Drug Taken. The amount of drug taken by the addict may be remarkably large. De Quincey in his "Autobiography and Confessions of an Opium Eater" remarked that at one time he took 133 drams (over 500 cc) of tincture of opium daily. This is the equivalent of 4.7 grams of morphine, or 300 times the single therapeutic dose. One of Light's patients (1929) employed 4.5 grams of heroine daily by subcutaneous injection. The average daily allotment of heroine, cocaine or morphine more often ranges between 0.5 and 1.8 grams. The patient cannot be trusted to give an honest report on his dose because he feels that by exaggerating his needs he will more easily succeed in obtaining what he desires. In estimating the daily requirements of an addict it is necessary to establish the amount which keeps him comfortable and prevents withdrawal symptoms.

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* The designation of cocaine as a narcotic is inconsistent with the definition given on page 27, and merely refers to the inclusion of cocaine under the Federal Narcotic Regulations.

Mechanism of Narcotic Addiction. The cause of addiction to certain drugs is unknown. Many theories have been advanced but none is entirely satisfactory (*see* review by Tatum and Seevers, 1931). Intimately connected with the cause of drug addiction is the problem of tolerance. Tolerance to opium alkaloids cannot be attributed to increased excretion, decreased absorption or accelerated destruction. Unexplained is the fact that the addict is tolerant to nine or more times the dose which he requires to prevent symptoms of abstinence, and that such a dose does not increase the interval before the drug is again requested. In addition to manifesting marked tolerance to morphine, the addict is psychically and physiologically dependent upon the chemical for his stability and well-being. The term *habituation* refers to the psychic and emotional dependence on the drug, whereas the term *dependence* signifies the more basic physiological need for the narcotic. When morphine is withdrawn, a characteristic abstinence syndrome appears which is a psychosomatic complex of signs and symptoms clearly showing both the psychical and organic dependence of the addict on the drug. The psychic component of addiction may be more prominent than the physical, and the intensity of habituation is thus not necessarily proportionate to the severity of dependence (Himmelsbach, Eddy and coworkers, 1938). Addiction is particularly likely to occur to those narcotics causing analgesia of short duration, which must therefore be given at frequent intervals, and which produce euphoria of long duration in relation to the period of relief from pain.

Also closely concerned with the mechanism of addiction are the nature and physiological basis of the withdrawal symptoms. If one could describe with certainty the pathological and functional changes which occur in the addict when his drug is withdrawn and correlate these adequately with the symptoms which occur, the alterations caused by morphine in the tissues of the addict would yield more readily to study. The exhaustive clinical investigation of Light and associates (1929) offers little promise in this regard. Their findings do not explain the train of symptoms which ensues when the opiate is withdrawn.

Light and his coworkers have therefore been forced to the conclusion that withdrawal symptoms may be largely hysterical. However, others disagree and believe that there is an organic basis for such symptoms. They point out that neurocytological changes in the brain of addicts have been described but these do not appear to be constant or specific. Disturbances in water metabolism and the autonomic nervous system have also been advanced as the basic alterations in addiction, but these would seem to be the consequence and not the cause of the phenomenon. Tatum, Seevers and Collins (1929), on the basis of experiments on monkeys, have proposed that withdrawal symptoms represent the unmasking of hyperexcitability produced by the continued use of morphine. This interesting suggestion needs corroboration.

The effects of chronic morphinism and morphine withdrawal in chimpanzees on various physiological and behavioral functions have been described in the monograph by Spragg (1940).

Symptoms and Effects of Morphine Addiction. The popular conception of the morphine addict as a cunning, cringing, malicious and degenerate criminal who is shabbily dressed, physically ill and devoid of the social amenities could not be farther from the truth. When the addict is properly dressed and fed and receives his daily drug requirement, he cannot be distinguished from other persons. He remains in excellent health and suffers no inconvenience or physical abnormalities unless he ceases to take the drug. The euphoria experienced at first soon disappears unless the dose is continuously elevated. Some addicts practice the habit for the euphoria they obtain, but an appreciable number do it only to escape from the distress which quickly follows withdrawal. Brilliant and famous persons have been narcotic addicts and their affliction often has remained unknown even to their closest associates. The only adequate test of morphine addiction is the occurrence of withdrawal symptoms upon cessation of the narcotic.

Excellent health and productive work are thus not incompatible with narcotic addiction. This holds true particularly for morphine because, as already stated, tolerance is not developed to the stimulant effect of heroine and cocaine, and addicts to these drugs are often dangerous characters. Extensive clinical and laboratory examinations of a large number of hospitalized persons addicted to morphine for from five to 20 years failed to reveal change in any tissue, fluid or function of the body which definitely differentiated the addict from the normal non-addicted individual (Light and collaborators, 1929). The only departures from normal were the tendency to a low red blood cell count, a high white blood cell count, a somewhat increased blood cholesterol and lactic acid, and a decreased phosphate level of the blood. Also there were noted a slight delay in gastric secretory response to a test meal, albuminuria in one of six addicts, and a lag in the return of the blood sugar to normal following oral ingestion of dextrose. In a well controlled study, Williams (1939) observed that morphine addiction in man is associated with hydration of the blood to a moderate degree.

Ill health, crime, degeneracy and a low standard of living are the result not of the pharmacological effects of morphine but of the sacrifice of money, social position, food and self-respect in order to buy the daily dose of drug. Inasmuch as narcotics are ordinarily obtained through illicit channels, the cost is high. It is difficult for a normal person to appreciate how completely the desire and necessity of maintaining an adequate supply of narcotic dominate the entire thought and action of the addict and become the major purpose of his existence.

Diagnosis. The facts cited leave little doubt that the addiction to morphine is often difficult to recognize. Some habitués experience severe constipation alternating with diarrhea. Many, but not all, show contracted pupils. There may be scars and abscesses of the skin due to repeated infections if the drug has been injected without aseptic technic. The distribution of these scars is over those skin areas to which the patient has ready access, that is, anteriorly; but this is true only if the drug is self-injected. The physician's suspicion should also be aroused if a patient fails to respond characteristically to a dose of morphine which is ordinarily sufficient to cause depression. In the last analysis, the only true diagnostic test for addiction is the occurrence of a fairly typical train of abstinence symptoms upon withdrawal of the drug.

Withdrawal Symptoms. The character and severity of the withdrawal symptoms depend on many factors. These include the type of treatment instituted, the dose of narcotic and interval used, the duration of addiction, and especially the health and personality of the patient. If it is absolutely clear to the addict that regardless of his complaints, pleas and demands he will not receive an opiate, the course of withdrawal is much easier. The purpose of the cure is often important in determining the cooperativeness and symptoms of the patient. For example, those forced against their will to undergo therapy are difficult to manage. On the other hand, many confirmed addicts "take the cure" in order to be able to start all over again with a dose which is small and therefore cheap, and which again produces the euphoria which tolerance prevents them from experiencing. Such patients will plead for a "pick-up" dose of one-quarter grain of morphine about the third or fourth day after withdrawal. If they experience euphoria from this small dose they know that their tolerance is broken and that their susceptibility to morphine is restored. They then continue with the remainder of the treatment quietly and cooperatively. Their object has been attained (Light and associates, 1929).

Although psychic factors are undoubtedly important in determining the character of withdrawal symptoms, some of the signs and symptoms are so constant and severe as to suggest a deeper basis than hysteria, despite the fact that such a basis remains undisclosed. Symptoms start within four to 12 hours or longer after the last dose of morphine is omitted, depending on the interval used by the addict. They are usually quite severe within 48 hours, reach their peak in 72 to 96 hours and are definitely on the decline by the fifth day. Symptoms of morphine abstinence have ceased within five days to two weeks, usually having disappeared by the eighth day. At the height of the effects of withdrawal, tolerance is still present as can be shown by the injection of the dose to which the patient was accustomed. Such an injection relieves all subjective distress and completely restores the equanimity of the patient within five to 30 minutes. After withdrawal symptoms have ceased, tolerance has disappeared and death may readily occur from taking the former large doses.

The first symptoms to be noted are lacrimation, yawning, sneezing, sweating, anorexia and tremor. These are followed by voluble expressions of desire for the drug, restlessness, psychic depression, irritability, muscular weakness, mydriasis, fever and increased respiratory rate. There then follow increasing irritability, insomnia, marked anorexia, yawning which becomes violent, severe sneezing, excessive lacrimation and coryza, and hoarseness. Weakness and depression are pronounced. Marked chilliness alternating with vasomotor disturbances of flushing and excessive sweating are characteristic and annoying. Vomiting may occur, and colic and diarrhea are usually prominent. The chilliness experienced by the addict has its physical counterpart in the skin which shows striking pilomotor activity and resembles the skin of a plucked turkey. This is the origin of the expression "cold turkey" to signify abrupt drug withdrawal without substitution therapy. Often at the end of the first eight hours or thereabouts the addict falls into a deep sleep, known as a "yen," which may last for from eight to 12 hours, but from which he awakens more restless and miserable than before.

The failure to take fluid and food, coupled with vomiting, sweating and diarrhea, results in weight loss, dehydration and acidosis. Muscle pains in the abdomen, back and extremities are also quite characteristic and are particularly severe in the popliteal region. There may be rigidity in the right lower quadrant and this, combined with abdominal pain and a commonly occurring leukocytosis, may simulate appendicitis. Severe muscle tremors and twitchings, headache, diplopia, delirium, occasionally mania, and seminal emissions or orgasms complete the picture. Sometimes cardiovascular collapse may appear and this may require the administration of morphine to prevent death. The cardinal features of the abstinence syndrome have been summarized in Table 10, from the publication of Himmelsbach, Eddy and associates (1938), which lists the signs in their approximate order of appearance but chiefly with regard to their significance for an estimation of the intensity of the withdrawal syndrome.

TABLE 10

THE ABSTINENCE SYNDROME

(Himmelsbach, Eddy and associates, 1938)

MILD (+)	MARKED (+++)
Yawning	Fever
Lacrimation	Increase in respiratory rate
Rhinorrhea	Restlessness
Perspiration	Insomnia
MODERATE (++)	SEVERE (++++)
Muscle tremor	Vomiting
Gooseflesh	Diarrhea
Loss of appetite	Weight loss
Dilated pupils	

As symptoms subside, the patient begins to eat, drink and sleep and rapidly regains his composure and weight. Physical and laboratory examinations during and after withdrawal reveal little information to which the dramatic symptoms can be ascribed. During withdrawal, there occur some weight loss, a polymorphonuclear leukocytosis, a slight rise in blood cholesterol, often some measure of anhydremia, and a reduction in performance of physical fitness tests. When morphine is readministered or when well-being has returned after completion of treatment, re-examination of the patient shows little change in these findings which therefore offer a meager basis on which to explain the symptoms. Following readministration of morphine, however, there does occur uniformly a rise in the percentage oxygen saturation of the venous blood, the significance of which is not immediately apparent (Light and collaborators, 1929).

Those who have had most experience with addicts during the abstention period cannot decide whether the symptoms are psychic or organic in origin. The diplopia, muscle twitchings and leukocytosis, for example, certainly suggest an organic basis. To quote Light and coworkers (1929), "It has been our frequent experience to leave the wards with the firm conviction that these men are not organically sick, the whole picture being an emotional one, and that the viciousness attached to the picture could best be coped with in penal institutions. Just as frequently we have entered the ward and found these men suffering with violent muscle twitches, vomiting, perspiration and yawning and showing such a sickly appearance that we have been convinced that there must be an organic basis for their apparent suffering."

Therapy of Drug Addiction. The management of narcotic addiction is a highly specialized problem and only the broad outline can be given here. Combined medical, nursing and psychiatric therapy are essential for success. Withdrawal treatment is undertaken as a rule only by those with special training in this field. The patients are hospitalized or placed in special retreats which are available for this purpose. The Federal government maintains two hospitals for the study and management of narcotic addicts under the auspices of the United States Health Service, at Lexington, Kentucky, and at Fort Worth, Texas. It is to be hoped that other similar facilities will soon be provided.*

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* The necessary information concerning voluntary admission of narcotic addicts to these two government hospitals can be obtained from the Surgeon General of the United States Public Health Service, Washington, D. C. Only citizens who are addicted to opium and coca leaves or their derivatives, or to peyote or Indian hemp are eligible. The cost for those who can pay is $1 per day. Confinement cannot be made without the patient's consent. Facilities for women are to be available early in 1940.

The patient is carefully examined to determine whether his physical condition is sufficiently good to warrant withdrawal therapy. Patients with renal, cardiac and other serious organic disease are poor risks, as are also pregnant women or debilitated persons. Careful search is made of all body orifices for contraband to insure that no smuggling of narcotics has been accomplished. Every conceivable scheme is used by confirmed addicts to insure a supply of opiate should the abstention symptoms prove too harsh. For example, they will have letters sent to them, the paper of which has been saturated with morphine, dried, ironed and inscribed with an innocent message; or the postage stamp may conceal the drug placed underneath (Light and associates, 1929). Therapy is especially difficult in those who are also addicted to alcohol or cocaine as well as to opiates.

Withdrawal may be abrupt, rapid or slow. Gradual withdrawal is probably less rigorous in those individuals who are not particularly robust. There is no such thing as a gradual reduction of dosage which will be imperceptible to the patient. A dose is soon reached below which craving and other symptoms appear. One can, however, reduce the dose far below the customary one used by the addict before craving is noted. This lower level is usually around 30 mgm regardless of the fact that much larger amounts were taken. When doses below 30 mgm are given, the patient becomes difficult to manage. Regardless of the method selected, symptoms do not occur in full force until several hours after the last dose of drug has been administered and then they continue to increase in severity for the next three days.

In addition to careful nursing, the patient should receive sedatives to promote sleep. Chloral hydrate is one of the most satisfactory for this purpose but the barbiturates and bromides may also be used. The taking of fluid and food should be encouraged. The belladonna alkaloids, atropine and scopolamine, have been widely employed in large doses in an attempt to mitigate the abstinence symptoms not only by central depression and amnesia but also by depression of structures innervated by cholinergic nerves, especially the bowel and secretory glands. Those advising the use of belladonna drugs believe that the distress of withdrawal is largely due to excessive stimulation of the vegetative nervous system. Comparative clinical studies by Lambert (1931), however, cast considerable doubt on the value of atropine and scopolamine. These agents tend to lessen the gastro-intestional symptoms but appear to aggravate many others. Exercise and warm baths tend to promote sleep, and nitrites may aid in the relief of muscle cramps.

Several routine systems of treatment exist and bear the names of their initiators such

TABLE 11

COMPARISON OF RESULTS OBTAINED IN THE ADDICT UPON WITHDRAWAL OF MORPHINE AND OF CERTAIN DERIVATIVES OF MORPHINE PREVIOUSLY SUBSTITUTED FOR IT

(Arranged from the data presented by Himmelsbach, Eddy, and associates, 1938)

DRUG	NO. OF CASES	NO. OF DAYS OF COMPLETE SUBSTITUTION FOR MORPHINE	DOSAGE OF SUBSTITUTED DRUG			ADEQUACY OF ADDICTION SATISFACTION BY SUBSTITUTED DRUG	ABSTINENCE SYNDROME FOLLOWING WITHDRAWAL OF SUBSTITUTED DRUG		
			No. of injections per day	Duration of dependence satisfaction	Daily amount in relation to morphine **		Onset	Intensity in relation to morphine	Duration ‡
				(hours)			(hours)		(days)
Morphine	±100	....	4	±6	....	....	±14	....	±8
Codeine	7	8 to 14	4	6 or more	±5	Adequate †	±20	As severe	±8
Dihydromorphinone (Dilaudid)	7	12 to 17	4 *	±3	±0.25 *	Complete	±10	As severe	±5
Methydihydromorphinone	7	7 to 10	8 or 9	±2	±0.2	Complete	± 3	As severe	5 to 7

* A sufficient dose of dilaudid was given so that not more than four injections daily were necessary. Smaller doses satisfied dependence for not much longer than three hours.

† Satisfaction of dependence, that is the relief of physiological disturbances and the disappearance of pains, aches, etc., was accomplished by substitution of codeine for morphine; but psychical manifestations of abstinence were not completely relieved. The patients were not as emotionally content on codeine as on morphine and claimed that there was "something missing."

‡ Number of days before the severe symptoms of the abstinence syndrome were spent. Return to normality required many weeks or several months.

** The actual amounts of drug used are not shown but rather the average amount needed per day by the group as a whole, in order to maintain psychic and physiological stability, in relation to the average amount of morphine required by that group prior to the substitution.

as the Pettey (1909), Lambert-Towns (1909) and Sceleth (1916) methods. They have in common the free use of intense purging and full doses of belladonna alkaloids. All these systems are successful but it is perhaps best to adapt the treatment to meet the needs of the individual patient.

Codeine substitution was thought for a time to afford a better therapy than any so far devised (Lambert, 1931). In brief, it consists in the withdrawal of morphine at the rate of 10 per cent per day over a period of ten days, and the substitution of ascending doses of codeine for the morphine. The dose of the substituted alkaloid starts at 30 mgm every four hours and is increased daily until the largest dose of codeine to be given is reached on the fifth day, 300 mgm every four hours. Codeine is continued at this dose level until three days after the last dose of morphine, and then it is decreased in amount as rapidly as the discomfort of the patient permits. It has been claimed that patients suffer little under this regimen and are quite manageable. Withdrawal from morphine by means of codeine substitution, however, probably has no distinct advantages. Indeed, reference to Table 11 indicates that withdrawal from the substituted codeine requires as long a period and is just as severe as withdrawal from morphine. Furthermore, the patient while on codeine does not experience relief of psychical manifestations of abstinence.

From time to time, various cures are advanced for morphine addiction or the therapy of withdrawal symptoms. "Narcosan" and sodium thiocyanate are two such proposals which have been entirely discredited. Insulin has also been recommended for addiction therapy but evidence of its value or rationale is meager.

After withdrawal symptoms have disappeared, rehabilitation of the patient is necessary to insure success of the cure. Wide personality and environmental adjustments are often required to remove the basic cause of the addiction. Cures are often temporary and the relapse rate, especially among confirmed addicts, is high. Great care should always be observed in using any opiate in a patient formerly addicted to narcotics. The treatment of addiction to heroine, dilaudid, cocaine and alcohol follows the general plan outlined.

For many of the facts and views on the important medical and social problems of narcotic addiction, the interested reader is referred to the books by Terry and Pellens (1928), Light and co-authors (1929), and Small and associates (1938).

Therapeutic Uses of Opium and Its Alkaloids

Sydenham, whose appraisal of opium is given at the opening of this discussion, also remarked that without opium few physicians would be sufficiently callous to practice therapeutics. Osler frequently referred to morphine as "God's own medicine." These statements serve to emphasize the *indispensable* nature of opium alkaloids, especially for the relief of pain. However, the fact that morphine and its derivatives are capable of causing addiction is a serious drawback and the physician must constantly be on guard lest his patient become addicted to the opiates.

There are a few simple procedures which will greatly decrease the likelihood of addiction. The physician should never employ a narcotic when another drug will accomplish the same end. In other words, morphine and its congeners are reserved only for certain definite indispensable uses which will be outlined. The patient is not to be informed of the fact that he is receiving an opiate. The hypodermic use of morphine is never to be entrusted to the patient himself. When a supply of narcotic is prescribed, it is made sufficient to last only until the patient is next seen by the physician, and this should be a short interval. The opiate is to be discontinued at the earliest possible moment. If the patient has received the drug for several days, he must be watched closely after cessation of therapy to discover whether he is addicted. In prescribing and dispensing of narcotics, it is incumbent upon the physician to be fully acquainted with the Federal and state laws regulating this field. These are briefly summarized on page 1324.

In using opiates, it is to be remembered that symptomatic therapy alone is being administered and that the underlying pathology is still present. Also the depressant actions of opium alkaloids may obscure the symptoms or progress of the disease, especially if the drugs are used unwisely. The proper employment of these agents, nevertheless, is of great assistance to the practitioner in performing his chief duty, namely, the relief of pain and suffering.

Certain aspects of the therapeutics of opium alkaloids have already been discussed. The uses of papaverine have been presented. The clinical differences between morphine, codeine, heroine and dilaudid in regard to pain, euphoria, depression and duration of action have been described; certain other clinical features of codeine, heroine, pantopon, and dilaudid have also been mentioned. The idiosyncrasies and variations in response to opium alkaloids have likewise been outlined.

Local Uses of Opiates. With the exception of the local application of dionine to the conjunctiva for the therapeutic hyperemia it produces, there are no rational local uses of opium alkaloids. These drugs are not local anesthetics and they relieve pain only by their central actions. Indeed, irritation and vesication may result from opium plasters, ointment or washes applied to the skin or mucosa.

Sudorific Action. Although morphine produces some degree of sweating, it is a very poor diaphoretic when compared with pilocarpine. The sweating caused by Dover's powder is mainly due to the ipecac content. The use of this powder as a diaphoretic for aborting the onset of "colds" due to exposure has the same rationale as suggested under alcohol.

Pain. *The opium alkaloids have no rival for the relief of pain,* and when suffering cannot be allayed by non-narcotic analgesics or other therapeutic measures, morphine may be considered indispensable. The types of pain obtunded most readily by morphine have already been discussed. This pain may arise directly from smooth muscle or nerve tissue or indirectly through traumatic, infectious or inflammatory processes. It bears re-emphasis that the analgesic action of this alkaloid is so specific that pain can often be considerably relieved by doses (five to 10 mgm) which cause little stupefaction or respiratory depression. All too frequently amounts are prescribed which produce unnecessary depression or sleep rather than specific analgesia. In this regard, dilaudid apparently has an advantage over morphine. In some cases in which dilaudid is used to abolish pain, it may be necessary to prescribe a sedative drug in addition if sleep is also desired. When both analgesia and sleep are required, morphine has no equal.

Pain from all parts of the body is dulled by the central action of the morphine alkaloids. The more severe the pain, the larger is the dose of opiate required and the greater the amount of drug that can be tolerated. Thus for the severe pain of coronary thrombosis, two to four times the usual therapeutic dose of morphine may be given without danger of seriously embarrassing the respiration. This is in keeping with the general principle that the degree of stupefaction caused by a given amount of a depressant drug is directly proportional to the level of reflex excitability of the nervous system. It is not unusual to administer within an hour from 45 to 60 mgm of morphine in divided portions for patients with excruciating pain. However, caution is required in the administration of these large total doses, especially when they are used for severe pain of a type which may suddenly lessen in severity or even disappear entirely. For example, the pain of coronary occlusion or of renal or biliary colic may rapidly decline spontaneously. If the patient has been given a large amount of morphine, he may show signs of morphine poisoning. Close observation of the patient and proper spacing of the doses of morphine will usually prevent such an occurrence.

Pain is a chief diagnostic sign for the physician and its total abolition may seriously handicap the discovery of the nature of the patient's illness. It has been said of morphine that, "It not only puts the patient to sleep but also puts the physician to sleep." While it is generally unwarranted to make the diagnosis at the expense of unbearable pain, nevertheless there are certain conditions in which opiates are not usually prescribed until the diagnosis has been made and the permission obtained for operation, should the latter be necessary. These conditions especially comprise what is known as the *acute surgical abdomen.* For example, no single cause, other than the use of a cathartic, is responsible for more complications or deaths from acute appendicitis than the misuse of opiates.

Nevertheless, it has been claimed that the skillful use of morphine may sometimes aid considerably in the diagnosis of acute abdominal conditions. The patient who is restless, apprehensive and in severe pain often cannot give a satisfactory or correct history. Rigidity of the abdominal muscles may prevent an adequate physical examination. This rigidity may be due not only to the reflex spinal component as a result of an inflamed viscus but also to a cortical component secondary to intense pain. Morphine in analgesic doses abolishes the cortical component and leaves the spinal reflexes unaffected (Zierold, 1935). Morphine, in expert hands, may thus be employed to aid in abdominal diagnosis, for which purpose it has been injected intravenously (15 mgm) to obtain analgesia and cooperation quickly (Singer, 1936). Naturally, a base line history and physical examination are necessary and the patient must be followed closely.

In patients with pain due to *neoplastic growths* or chronic hopeless diseases, the use of morphine alkaloids should be reserved until non-narcotic drugs no longer give relief. Then codeine should be employed in combination with non-narcotic sedatives and analgesics and the doses increased until pain can no longer be controlled without morphine or dilaudid. The doses should be kept as low as possible so that maximal relief may be given for the longest possible period. Tolerance develops and one wishes to reserve a margin of susceptibility in order to cope with the terminal stages when pain may be excruciating. In other words, "The physician should use morphine as a miser spends his gold." If necessary, of course, morphine is given without stint. Addiction is expected and justifiable in patients with malignant growths. When opiates are unsatisfactory, nerve blocking by injections of alcohol or chordotomy may be required if the nature of the lesion allows. In most cases the euphoria, tranquillity and relief of pain afforded by the wise use of narcotics are a blessing to the patient and his family and death is made easy and comfortable.

For the relief of pain arising from spasm of smooth muscle, as in *renal or biliary colic,* morphine has no equal. Other measures including antispasmodics such as atropine, nitrites and heat may be employed first, but if they are ineffective opiates must be used. Morphine is also indispensable for the relief of pain due to *acute vascular occlusion* whether this be peripheral, pulmonary or coronary in origin. Papaverine may be given advantageously in embolism of peripheral or pulmonary arteries. In painful acute *pericarditis, pleurisy* and spontaneous *pneumothorax,* morphine is likewise indicated. Carefully chosen and properly spaced doses of codeine or morphine may occasionally be necessary in *pneumonia* to control pain, dyspnea and restlessness. Traumatic pain arising from *fractures, burns,* etc. frequently requires morphine, and *shock* whether due to trauma or poisons often necessitates the administration of opiates not only to relieve pain but also to control restlessness and to allow sleep.

The use of opiates in *obstetrical analgesia* is a highly specialized field requiring considerable experience and sound judgment to insure safety. Morphine has been combined with scopolamine in "twilight sleep" but this mixture is not used nearly as much as formerly. Various combinations of barbiturates, scopolamine, paraldehyde and the inhalation anesthetics have made morphine less popular in obstetrical work. The opiates are powerful respiratory depressants. The fetus is especially susceptible to morphine which greatly increases the incidence of asphyxia in the newborn. The use and value of morphine in *preanesthetic medication* are fully presented elsewhere (page 46). Post-operatively, narcotics may be employed to control pain and discomfort for the first one to three days, but if prescribed indiscriminately they may obscure the outcome of surgery and the course of recovery, as well as prevent the early recognition of complications. For *headache,* codeine may be effectively combined with analgesics like salicylates or acetanilid. Morphine is not used in migraine unless all other measures, including ergotamine, have failed. Great care should be exercised to prevent addiction.

Sedation and Sleep. Whenever possible, drugs other than narcotics are to be prescribed for sedation, tranquillity or sleep. In many cases, however, the opiates must be resorted to in order to provide the necessary relief from insomnia, restlessness or excitement and thus conserve the patient's strength. The ordinary nonnarcotic somnifacients such as bromides, chloral hydrate and barbiturates are not analgesic and when sleeplessness is due to *pain* or *cough,* opiates are often required. In certain forms of *delirium, mania,* and *psychoses* and in the hyperexcitable states caused by *thyrotoxicosis* and certain *encephalopathies,* opium alkaloids may be needed. In these conditions smaller doses of morphine produce sedation than are necessary when pain is also present. When sleep and relief from restlessness and apprehension are absolutely essential as in *threatened abortion, internal hemorrhage, congestive heart failure* and *massive pulmonary hemorrhage,* morphine provides a valuable therapeutic agent.

Cough and Dyspnea. *Cough,* especially when unproductive and irritating, interferes with rest and sleep and may be painful. It can also result in cardiac strain and cause pulmonary or cardiovascular accidents. The types, mechanism and physiological usefulness of coughing are presented elsewhere (page 815). The opiates comprise the so-called anodyne expectorants, and codeine in particular deserves preference for quieting an overactive cough reflex. The antitussive dose is kept small (five to 10 mgm) because repeated medication may be necessary. The uniformly effective oral dose of codeine for cough is about 10 mgm (Davenport, 1938). Large doses of codeine (over 60 mgm) may actually increase the irritability of the respiratory and cough mechanism. Codeine can be effectively incorporated in an expectorant cough mixture for a dry, irritating cough with the object of stimulating secretion of mucus and yet reserving the cough reflex for productive expectoration. Coughing should not be unnecessarily depressed, especially if bronchial secretion is profuse, because drainage will then be insufficient and complications may ensue. Small amounts of codeine, or of morphine (two to four mgm), will decrease the frequency of coughing without altering significantly the respiratory minute volume.

Certain forms of *dyspnea* yield only to opiates. Especially in this category is the dyspnea of acute left ventricular failure and pulmonary edema. In *bronchial asthma,* morphine is not indicated because of the danger of addiction, because morphine tends to depress respiration and constrict bronchioles, and due to the fact that asthmatics may be allergic to the drug. Death may occur from its use in asthma.

There is no good evidence that the use of codeine or papaverine shortens the duration of the "common cold." Opiates tend to dry the mucosal lining of the throat and nose but other measures such as atropine can accomplish this end. If headache and pain require relief, non-narcotic analgesics should first be employed. If the symptomatic improvement afforded by codeine encourages the patient to be ambulatory when he should be in bed, the medication has done harm by increasing the chances for complications and the infection of other individuals.

Antiperistaltic Action. The action of the opium alkaloids in checking peristalsis and causing constipation is desired in a variety of diseases and syndromes. These include exhausting diarrheas and dysenteries, gastro-intestinal hemorrhage, perforation or rupture of abdominal viscera, peritonitis, and rectal tenesmus. Where diarrhea is caused by acute food or drug poisoning, opiates are not prescribed until the offending agent has been evacuated by saline cathartics. Traditionally opium preparations rather than the alkaloids are prescribed, either the tincture (0.5 to 1.0 cc) or the powder (30 to 100 mgm) being used.

Anticonvulsant Action. The use of morphine in convulsive disorders such as strychnine poisoning, tetanus, status epilepticus, etc. is invalid and preference should be given to the soluble barbiturates, paraldehyde and chloral hydrate. The motor excitability of the cortex is depressed only by large doses of morphine which in turn cause an increase in reflex excitability of the spinal cord. Morphine sulfate, however, is given in conjunction with chloral hydrate in the Stroganoff therapy for impending eclamptic convulsions, two doses of morphine (15 mgm) being injected at an interval of four hours.

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CHAPTER 13

ANALGESICS AND ANTIPYRETICS

I. THE SALICYLATES, CINCHOPHEN AND NEOCINCHOPHEN

The growing scarcity and the consequent high price of quinine during the last third of the 19th century motivated the search for synthetic substitutes. As a result, a large number of compounds were introduced into medicine and, although they differed considerably from quinine both chemically and in their lack of antimalarial efficacy, they shared with cinchona the ability to produce antipyresis and analgesia. Several have survived and proved their usefulness, not so much as antipyretics but rather as analgesics. They are also useful in the treatment of acute rheumatic fever and gout.

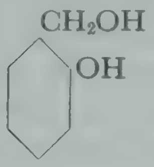
The analgesic-antipyretic drugs may be divided into three classes, as follows:

I. The salicylate-cinchophen group.
II. The paraminophenol derivatives—acetanilid and acetophenetidin.
III. The pyrazolon derivatives—antipyrine and aminopyrine.

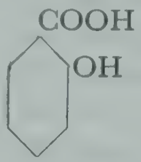
THE SALICYLATES

History and Source. *Willow bark (Salix alba),* the antipyretic property of which was known to the ancients, yields a bitter glycoside called *salicin,* first discovered by Leroux in 1827. On hydrolysis, salicin liberates glucose and *salicylic alcohol* (saligenin). Piria, in 1838, made *salicylic acid* from salicin. Six years later, salicylic acid was prepared from *oil of gaultheria* (oil of wintergreen) by Cahours. The synthetic manufacture of this acid from phenol was accomplished in 1860 by Kolbe and Lautemann. *Sodium salicylate* was used for the first time as an antipyretic by Buss in 1875, and in the following year its value in *rheumatic fever* was discovered by Stricker. *Phenylsalicylate* was introduced into medicine in 1886 by Nencki, and *acetylsalicylic acid* (aspirin) in 1899 by Dreser. The name aspirin comes from "spirsäure," the German word for salicylic acid. The synthetic salicylates soon completely displaced the more expensive compounds obtained from natural sources, being just as effective.

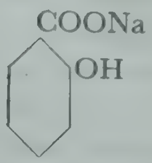
Chemistry. Salicylic acid (orthohydroxybenzoic acid) is so irritating that it can only be used externally and therefore various derivatives of this acid have been synthesized for systemic use. These may be grouped in two large classes—those which are *esters of salicylic acid* through substitution of the H in the carboxyl group, and those which are *salicylate esters of organic acids* in which the carboxyl group of salicylic acid is retained and substitution is made in the OH group. For example, aspirin is an ester of acetic acid. In addition, there are simple salts of salicylic acid such as the sodium and ammonium salts. These relations can be seen clearly from the following structural formulas:



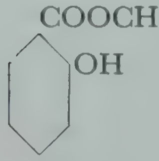
Salicylic Alcohol
(Saligenin)



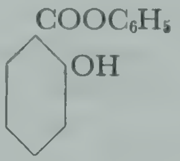
Salicylic Acid



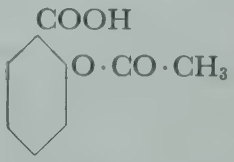
Sodium Salicylate



Methyl Salicylate
(Oil of Wintergreen)



Phenyl Salicylate



Acetylsalicylic Acid
(Aspirin)

All the above compounds are referred to collectively as the "salicylates" or the "salicyl" drugs. The salicylates will be discussed as a group, and major differences noted as occasion arises.

Relationship Between Chemical Structure and Action. Salicylates exert their typical effects by virtue of their salicylic acid content. Variations in solubility and propensity to cause local irritation are the main factors which determine the degree of usefulness of these chemicals. The ortho position of the OH is an important feature for the action of salicylate. Benzoic acid, C_6H_5COOH, shares many of the actions of salicylic acid but is much weaker. If a methyl group is added to the benzene ring of salicylic acid, *cresotinic acid* ($C_6H_3{\cdot}CH_3{\cdot}OH{\cdot}COOH$) is formed. At one time it was claimed, especially by the interested manufacturers of the more expensive natural salicylates, that cresotinic acid was a toxic contaminant in synthetic salicylates. Conclusive researches demonstrated that cresotinic acid was no more toxic than salicylic acid and did not "contaminate" synthetic salicylates. The efficacy of the different salicylates depends in part on the amount of salicylate liberated in the body, but not entirely on this factor. For example, the salicylic acid equivalents of the commonly used drugs in this group are within 10 per cent of each other and yet the therapeutic potency of acetylsalicylic acid and methyl salicylate is about 50 per cent greater than sodium salicylate. This also holds true for their toxicities and depends especially on factors of solubility.

Pharmacological Actions

Local. *Antiseptic Action.* The salicylates, especially salicylic acid, are weakly *bacteriostatic.* In this respect, their action resembles that of quinine and benzoic acid in that certain fermentation processes are inhibited, the growth of moulds and fungi is checked, the putrefaction of meat, urine and other substances is delayed, and unicellular organisms and leukocytes are paralyzed. In alkaline media, phenyl salicylate may have more pronounced effects due to the liberation of phenol.

Local Irritant Effects. Salicylic acid is quite irritating to skin and mucosa, and destroys epithelial cells. The keratolytic action of the free acid is employed for the local treatment of warts, corns, fungus infections and certain types of eczematous dermatitis. The tissue cells swell, soften and desquamate. The salts of salicylic acid are innocuous to the unbroken skin, but by release of the free acid the gastric mucosa may be irritated. Methyl salicylate (oil of wintergreen) is irritant both to the skin and gastric mucosa, and is used externally in liniments as a counterirritant.

Central Nervous System. *Antipyresis.* Salicylates lower body temperature. This action is usually rapid and effective in febrile patients, but is rarely demonstrable when the temperature is normal (Figure 21). This is the rule for most antipyretics. Normal regulation of body heat requires a delicate balance between heat production and heat loss (DuBois, 1936, 1937). The central nervous system, especially hypothalamic nuclei, plays an indispensable rôle in regulating the peripheral mechanisms concerned with the production and loss of body heat. Consequently, the hypothalamus has been termed the "thermostat" of the body. In fever, the balance between heat production and heat loss still persists except that the "thermostat" is set at a higher level. The salicylates act to reset the "thermostat" for normal temperature. Heat production is not inhibited but heat dissipation is augmented by increased peripheral blood flow and sweating. There is abundant evidence to show that the salicylates act mainly on the central nervous system and not peripherally on blood vessels or sweat glands. High section of the spinal cord prevents the antipyretic drugs from lowering the temperature of fevered animals. Sweating is so prominently associated with the use of salicylates that it has come to be looked upon as a major response. Marked sweating, however, does not occur unless there is fever, and the latter can be lowered with salicylates even if sweating is prevented by atropine. The salicylates also cause hydration of the blood (Barbour, 1921) and this facilitates both sweating and the radiation of heat. The metabolic rate and the respiratory quotient in normal persons are not directly altered even by large doses of salicylates. Heat production is therefore not depressed. In febrile patients, the metabolic rate is lowered by antipyretic drugs but this is consequent to the fall in temperature. (The metabolic rate increases seven per cent for every degree F. of fever.) The mechanism of antipyresis summarized here

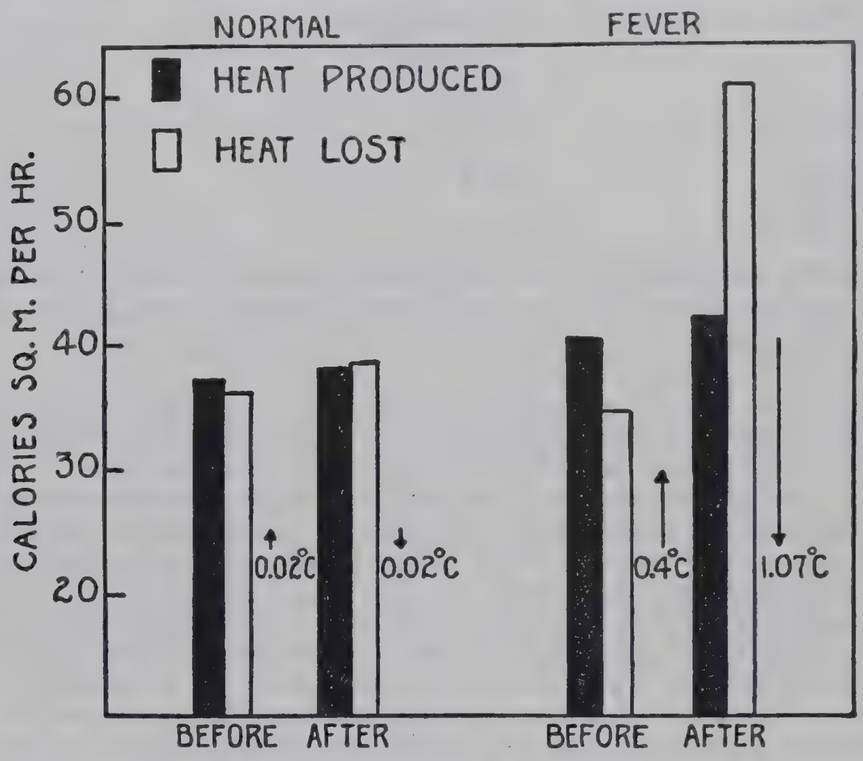


FIGURE 21. *The antipyretic effect of one gram of acetylsalicylic acid in normal persons and patients with fever.*

Arrow indicates direction and relative degree of temperature change. Note the insignificant antipyretic response in the normal person as compared with the febrile patient. Observe that the mechanism of antipyresis is an increased elimination rather than a decreased production of heat. (Figure constructed from the data of Barbour and Devenis, 1919, and Barbour, 1919.)

for the salicylates likewise applies to acetanilid, acetophenetidin, antipyrine and aminopyrine.

Analgesia. The salicylates are capable of alleviating certain types of pain. This is probably due to a central depressant action located in the optic thalami. That the site of action is not cortical is indicated by the fact that analgesic doses of the salicylates cause no mental disturbance, anesthesia or changes in modalities of sensation other than pain sense. Although some individuals claim to experience a mild hypnotic effect, this is certainly unusual and may be due to psychic factors. The types of pain amenable to relief by salicylates are headache, myalgia, arthralgia and other pains arising from integumental structures rather than from viscera. The significance of this is poorly understood. The salicylates are much inferior to morphine as analgesics. For example, the threshold for cutaneous pain as determined in human subjects by heat irradiation (Hardy, Wolff and Goodell, 1940) was increased only 35 per cent by 1.8 grams of aspirin taken orally, whereas an increase of 70 per cent was noted after 15 mgm of morphine sulfate administered intramuscularly (page 196).

Nerve endings are not anesthetized by salicylates, except saligenin (page 303). The relief obtained from the local application of methyl salicylate is due to the counterirritation. The use of aspirin locally for alleviating dental pain or sore throat has no rational basis.

Respiration. Average clinical doses of salicylates do not affect breathing, but toxic amounts first accelerate and deepen and finally depress respiration. In hypersensitive patients, the salicylates may cause dyspnea by precipitating an asthmatic attack.

Other Central Actions. In high doses, the salicylates have a toxic action on the central nervous system, consisting of stimulation followed by depression. The effects are similar to but milder than those produced by phenol, and are described under salicylate poisoning.

Cardiovascular System. Ordinary therapeutic doses of salicylates have no important cardiovascular actions. The peripheral vessels tend to relax with large doses, due to a direct effect on the smooth muscle of blood vessels. Toxic amounts depress the circulation directly and by central vasomotor paralysis. The concentrations necessary to injure the perfused heart are much higher than are obtainable in man even with toxic doses. There is no clinical or experimental evidence to support the opinion that the salicylates, especially aspirin, are injurious to the heart.

Gastro-intestinal Actions. The irritant effects of salicylates on the gastric mucosa may result in epigastric distress, nausea and vomiting. Large doses have been reported to cause stomach ulcerations in experimental animals, and melena has been observed from the use of aspirin in human beings (Hurst and Lintott, 1939). Vomiting after toxic doses of salicylates is not only due to local irritation but also to a central emetic action. Acetylsalicylic acid is less irritating to the stomach than is sodium salicylate, probably because it is relatively insoluble.

The salicylates cause an increase in the volume output of bile, but a decrease in the total cholate excretion (Schmidt and coworkers, 1938). This *choleretic action* is apparently due to a direct effect on liver cells. However, the experimental work in this field is contradictory and offers too insecure a basis for the clinical use of these agents as choleretics.

Metabolic Actions. *Uric Acid.* A prominent effect of therapeutic doses of salicylates, and especially of cinchophen, is to increase the urinary excretion of uric acid. The increase may be 30 per cent to 50 per cent, but is occasionally as much as 100 per cent. The blood uric acid is concomitantly reduced to one-third of its original level, although this is not invariably the case, for occasionally the blood uric acid may be elevated during the period of increased urinary excretion. Both the endogenous and exogenous uric acid fractions are affected, because the urinary changes occur in patients on purine-free diets as well as on high purine diets, and also the excretion of injected uric acid is hastened. The other constituents of the urine apparently are not simultaneously altered, so that the effect on uric acid excretion seems to be a specific one. If administration of the drug is stopped after a single dose or a few repeated doses, the uric acid excretion falls below the normal level and then rises slowly over a period of two to four days. Chronic administration may or may not be accompanied by a continuously elevated level of uric acid excretion, depending somewhat on the diet.

The mechanism by which the salicylates and cinchophen increase uric acid excretion is unknown. In general, three major theories have been advanced. The first explanation to be suggested was that the uric acid arose from disintegration of white blood cells. Careful clinical studies failed to support this view. The second theory proposes that these drugs increase uric acid formation or mobilization, as for example, by increased destruction of nucleoproteins, enhanced conversion from purines, inhibition of an uricolytic ferment, or mobilization of preformed uric acid from storage depots. The third theory maintains that the renal threshold for the purine is lowered. Presumably, the tubular reabsorption of uric acid is inhibited by the drugs, and hence the urinary excretion rises and the blood level falls. The renal basis of the uricosuria, though very probable, is yet to be fully established, and accurate uric acid clearance studies would be most helpful. Observations unexplained by this theory are the increased blood uric acid levels which occasionally occur, the increased biliary excretion of uric acid, and the apparent stimulation of purine metabolism by these drugs.

For details of this problem, the interested reader is referred to Hanzlik (1927) and Grabfield and Pratt (1931).

Actions on the Blood. Full therapeutic doses of salicylates do not materially alter the *alkali reserve* or the *pH of the blood*. Toxic doses of salicyl compounds, however, present a clinical picture which resembles diabetic or renal acidosis. The air-hunger which often occurs is similar to Kussmaul's hyperpnea and has been called "salicyl dyspnea." The mechanism is not understood, but it is thought to be due to a direct stimulatory action of salicylates on the respiratory center. On the basis of signs and symptoms alone, it may be difficult or impossible to distinguish salicylate poisoning from diabetic acidosis and coma. However, the laboratory findings indicate that the blood sugar level and carbon dioxide-combining power of the serum are little changed in salicylate poisoning whereas the former is elevated and the latter is decreased in diabetic acidosis. However, hyperpnea from salicylates may result in a carbon dioxide loss and a compensatory excretion of fixed base in the urine. The urines in both instances may reduce copper solutions, due to the false positive test for sugar given by salicylates. The ferric chloride test for acetoacetic acid in the urine shows a violet color after salicylates and not a positive Burgundy red reaction. If severe kidney damage occurs from salicylates, a frank renal acidosis may follow.

The number of *red and white blood cells* is not significantly changed by salicylate medication. The mechanism of the salicylate depression of leukocytosis in acute rheumatic fever is not understood, but is of considerable importance in judging the progress of the disease. Methemoglobin is not produced by salicylates and agranulocytosis has not been reported from their use.

Renal Effects. Moderate doses of salicylates cause a slight diuresis but it is likely that this is merely a salt effect. Large doses of salicylates, such as those employed in acute rheumatic fever, may somewhat diminish urine output, partly due to increased sweating but also because of renal impairment (Scott and Hanzlik, 1916; Hanzlik, Scott and Reycraft, 1917). The increase in blood urea, decrease in phenolsulfonphthalein excretion and albuminuria all indicate kidney impairment. Albuminuria is a constant finding in man after about three grams of salicylates have been taken. Casts, leukocytes and occasionally red blood cells may also be found after large doses. These renal effects disappear quickly without residual damage upon cessation of salicylate medication. Histological evidence of nephritis has been obtained both experimentally in animals and in cases of human poisoning. The alleged protective effect of sodium bicarbonate upon these renal changes has been disproved (Hanzlik, 1927). In some patients, large doses of sodium salicylate may so diminish renal function and urine output that the body weight increases. This has been termed "salicyl edema" but actual pitting edema does not develop.

"Antirheumatic Actions." The salicylates reduce the pain, immobility, swelling and inflammation of the joints in acute rheumatic fever, and this constitutes a major therapeutic use of these drugs. So efficient are the salicylates in this respect that they have been employed as a therapeutic test in the differential diagnosis of arthritis. The salicyl compounds and cinchophen are qualitatively alike in this antirheumatic action. The cardiac lesions and other visceral involvement in rheumatic fever, such as pleuritis, peritonitis, encephalopathy, chorea, and subcutaneous nodules, are not beneficially affected. The course and complications of the disease are also not influenced.

The mechanism of the action of salicylates in acute rheumatic fever is poorly understood. There is no evidence that immune bodies are increased, that a bactericidal effect is operative, that the uricosuric action is involved or that the salicylates have a general antiphlogistic action. The numerous studies with salicylates in experimental arthritis in animals have yielded contradictory results and are not directly applicable to rheumatic fever in human beings. The mechanism by which salicylates reduce joint effusions in rheumatic fever still remains an enigma. That the salicylates are not specific is shown by the fact that aminopyrine and cinchophen have a similar action. It is difficult to believe that the entire benefit can be attributed to the antipyresis and analgesia, although these two actions are the chief ones shared in common by agents effective in rheumatic fever.

Absorption, Fate and Excretion. *Absorption.* The salicylates are readily absorbed from the gastro-intestinal tract, including the rectum, and other mucosal surfaces of the body. In fact, rapid absorption may occur from the stomach itself (Bradley, Schnedorf and Ivy, 1936). The esters are hydrolyzed to salicylic acid only to a limited extent in the stomach and intestine and are chiefly absorbed as such into the circulation. Salicylic acid is rapidly absorbed from the intact skin, especially when applied in lard or lanolin. Methyl salicylate is likewise absorbed when applied cutaneously, but this route is too uncertain when systemic effects are desired. Gastro-intestinal absorption of this ester may be delayed many hours and therefore gastric lavage should be performed in cases of poisoning even though they are seen late.

Distribution and Fate. Shortly after absorption, salicylate can be identified in nearly every tissue and fluid. It is also found in pathological fluids, but the joint effusions in rheumatic fever contain no higher concentration of salicylate than does the blood. Hence there is no selective distribution of the drug to account for its therapeutic action.

The claim that free salicylic acid exists in the body and exerts a bactericidal action has not been substantiated. No free salicylic acid can be demonstrated in body tissues or fluids and the pH necessary for liberation of the acid is far lower than can occur in the body.

Excretion. Salicylates are excreted from the body by all channels, but especially by the urine. The urine may appear greenish brown after salicylate medication. Salicylate can be detected in the urine within 10 to 15 minutes after administration of a full therapeutic dose. The major excretion occurs within a few hours, but traces appear in the urine for three days or longer. Acetylsalicylic acid and methyl salicylate require a longer period for complete excretion than does sodium salicylate. About 20 per cent of salicylate is destroyed in the tissues. In patients with rheumatic and other fevers, the fraction destroyed may increase to 30 or 40 per cent. Simultaneous administration of sodium bicarbonate does not hasten salicylate excretion.

The esters of salicylic acid are excreted in the urine in part unchanged, from 10 to 35 per cent of acetylsalicylic acid being eliminated as such. Also, the urine of patients receiving the methyl ester has the odor of oil of wintergreen. Some of the salicylate is found in the urine in conjugated form, as the glycuronate and sulfate. Some oxidation of salicylate probably also occurs.

Preparations, Doses and Routes of Administration. The two most commonly used preparations of salicylate for oral administration are sodium salicylate and acetylsalicylic acid.

Sodium Salicylate, U.S.P., B.P., is a white or faintly pink powder, which is odorless and has a sweet, saline taste. It is quite soluble in water (1:0.9).

Acetylsalicylic Acid (Aspirin), U.S.P., B.P., is a white crystalline odorless powder. In moist air, it gradually hydrolyzes to salicylic and acetic acids. It is rather insoluble in water (1:300).

Ammonium Salicylate, U.S.P., *Strontium Salicylate,* N.F. and *Lithium Salicylate,* N.F., have no advantages over the sodium salt and are practically obsolete. All three are white, crystalline, odorless powders, and the first two are extremely soluble in water.

Phenyl Salicylate (Salol), U.S.P., is a white crystalline powder, having an aromatic odor and a characteristic taste. It is practically insoluble in water (1:6670) but is readily hydrolyzed in the alkaline intestinal juices to phenol (40 per cent) and salicylic acid (60 per cent). The phenol is readily absorbed and may cause carbolic acid poisoning if large doses of the ester are administered.

Methyl Salicylate (Oil of Sweet Birch, Oil of Wintergreen, Oil of Gaultheria, Oil of Betula), U.S.P., B.P., is obtained synthetically or by steam distillation of the leaves of *Gaultheria procumbens* or from the bark of *Betula lenta.* It is a colorless, yellowish or reddish liquid, having the characteristic odor and taste of wintergreen. It is slightly soluble in water but is miscible with alcohol. Methyl salicylate is so irritating when given orally that it is employed only for cutaneous counterirritation in the form of salves and liniments. Its use in low concentrations as a flavoring agent is discussed elsewhere (page 1318).

Salicylic Acid, U.S.P., B.P., is a white crystalline powder, odorless and tasteless when prepared synthetically. It is rather insoluble in water (1:460) but quite soluble in alcohol (1:2.7) and organic solvents. The acid is so irritating to the gastrointestinal tract that its use is reserved for local application as a keratolytic agent. Salicylic acid is a component of many ointments, some of which are official, as for example, *Whitfield's Ointment,* N.F. (page 1312), *Compound Salicylic Collodion,* N.F. (10 per cent salicylic acid in flexible collodion), *Paste of Zinc Oxide with Salicylic Acid* (page 861), N.F. and *Ointment of Salicylic Acid,* B.P. (two per cent of the acid in white paraffin ointment).

Several esters of salicylic acid other than the official ones already described are available but rarely used. They have no advantages over sodium salicylate and aspirin. Some of these are as follows: *Salysal*, N.N.R., the salicylic ester of salicylic acid; *Novaspirin*, N.N.R., methylene-citrylsalicylic acid; *Ethyl Salicylate*, N.N.R.; *Sal-Ethyl Carbonate*, N.N.R., the carbonic acid ester of ethyl salicylate.

The *dose* of the salicylates depends on the condition being treated. The usual dose of sodium salicylate or acetylsalicylic acid is from 0.3 to 1.0 gram (five to 15 grains). This may be repeated every three or four hours. In acute rheumatic fever, in contrast, intensive medication is employed and 1.0 gram or more of a salicylate is given every hour until early toxic effects ensue. Children are quite tolerant of the salicylates and require larger doses than calculated by their age or weight.

The *route of administration* is practically always oral. There is no advantage in and rarely a necessity for giving them parenterally. The intravenous use of these drugs is unjustified and dangerous. The only valid intravenous use of salicylates is in local varicosities for the purpose of sclerosing veins. Occasionally, the rectal administration of sodium salicylate (two per cent) in thin starch or acacia solution may be necessary in infants or when oral medication is not retained.

Nausea and gastric irritation from sodium salicylate may be avoided by the simultaneous administration of an equal or double amount of *sodium bicarbonate*. This protects against the release of salicylic acid. Alkali is not so necessary with acetylsalicylic acid, but the former opinion that sodium bicarbonate may increase the irritation from aspirin is not substantiated by clinical experience or laboratory experimentation (Schnedorf, Bradley and Ivy, 1936). Salicylates are conveniently taken in tablets or capsules rather than in solutions. Solutions of the sodium salt have a sweetish, nauseant taste which is difficult to mask completely. They also become discolored on standing and form a black precipitate if bicarbonate is present. Acetylsalicylic acid is quite insoluble, has many chemical incompatibilities, and is unstable in watery suspensions. It should therefore be prescribed alone in solid dry form.

Toxicology. The wide use of salicylates in medicine and their indiscriminate employment by the laity for every conceivable ailment provide the basis for numerous instances of toxic reactions. Fortunately, most of these poisonings are mild. Serious intoxication, however, does occur. In more than 30 reported cases in the eight year period following 1928, 50 per cent died (Bowen, Ronfa and Clinger, 1936). Balazs (1930), however, has reported that among 752 attempts at suicide with acetylsalicylic acid, only four ended fatally. *Idiosyncrasy* is also a cause of untoward response to the salicylates. Furthermore, the presence of renal impairment enhances the possibility of salicylate poisoning. As little as three grams of salicylate a day may cause severe intoxication in nephritic patients.

Acute Salicylate Poisoning. All the salicylates except salol cause the same type of intoxication. The *fatal dose* varies with the preparation. From 10 to 30 grams of sodium salicylate have caused death in adults but larger amounts have been ingested without fatal results. The fatal doses of acetylsalicylic acid and methyl salicylate are less than that of the sodium salt. As little as six cc of methyl salicylate may be fatal for children. In acute rheumatic fever, doses of salicylate are used which border on the toxic and under these conditions one expects to encounter early symptoms of poisoning.

Symptoms. Mild salicylate intoxication is termed "salicylism." This condition resembles cinchonism very closely, and is observed as a rule only when large doses are given repeatedly. When fully developed, the syndrome consists of headache, dizziness, ringing in the ears, difficulty in hearing, dimness of vision, mental confusion, sweating, thirst, nausea, vomiting, and diarrhea. The mechanisms of the auditory and the visual disturbances are the same as those described under quinine. The pulse and respiration may be accelerated, and there may also be skin reactions of an erythematous, scarlatiniform, pruritic, eczematoid, or desquamative character. Rarely, the cutaneous lesions may be bullous or purpuric in nature, and hemorrhages may occur from mucous membranes. Fever may be prominent, especially in children. Symptoms of central excitation are sometimes prominent in salicylate poisoning and resemble those caused by atropine. This stimulation has been called the "salicylic jag" and is characterized by restlessness, incoherent speech, excitement and occasionally mania, delirium and hallucinations. All the effects mentioned may occur when approximately 12 grams of salicylate have been given in divided doses over a period of 12 to 24 hours and disappear quickly when medication ceases.

Larger amounts of salicylates may cause disturbances in respiration referred to previously as "salicyl dyspnea" with a clinical picture resembling diabetic or renal acidosis. The kidney changes that occur after toxic amounts of salicylates have already been described. As poisoning progresses, central stimulation is replaced by increasing depression, stupor and coma. Cardiovascular collapse and respiratory depression ensue, and terminal asphyxial convulsions sometimes appear. Death usually results from respiratory failure after a period of unconsciousness.

Symptoms of poisoning by *oil of wintergreen* do not differ essentially from those just described. Poisoning occurs most frequently in children who mistake this aromatic oil for candy, and central nervous system symptoms and hyperpyrexia are prominent features. The odor of the drug can easily be detected in the urine and vomitus. Methyl salicylate should always be kept where children cannot gain access to it. Of 43 cases of poisoning in children reviewed by Stevenson (1937), 59 per cent were fatal. Poisoning by *salicylic acid* differs only in the prominent gastro-intestinal symptoms due to the marked local irritation. *Phenyl salicylate* poisoning is unique in that the most prominent symptoms are due to phenol which is liberated by hydrolysis in the intestinal tract.

Idiosyncrasy. Idiosyncrasy to salicylates manifests itself usually in the form of skin rashes and anaphylactic phenomena. These reactions are due to unexplained hypersensitivity and may occur after the first administration of a small dose of salicylate. However, the fact that one has been able to take salicylate without ill effects is no guaranty against the occurrence of allergic reactions to the drug. Acetylsalicylic acid is the compound most often involved. The skin lesions have already been described, and are frequently urticarial in nature. Allergic responses take the form of angioneurotic edema or asthma. If laryngeal swelling occurs, alarming asphyxial symptoms may develop. Edema of the eyelids, tongue, lips, face and intestinal tract is not uncommon and an erysipelatous swelling of the entire face may occur. Most of the patients who react badly to aspirin have a history of allergic disease, especially asthma. Over two-thirds of the allergic reactions to acetylsalicylic acid are due to asthma, and death may occur. One should therefore observe care in prescribing aspirin for patients with asthma, especially if they also have nasal polyps (Prickman and Buchstein, 1937). Individuals with idiosyncrasy to aspirin should be told of this fact and warned against taking patent medicines which often contain this drug. The skin tests are of no value in anticipating hypersensitivity, and may even provoke a severe reaction in some patients.

Treatment. The treatment of salicylate poisoning is purely symptomatic. Gastric lavage is performed to remove any poison still in the stomach, and magnesium sulfate is given to hasten unabsorbed salicylate through the intestinal canal. Fever may be counteracted by alcohol sponges. A liberal supply of fluid and sodium chloride is essential to offset the loss through vomiting, diarrhea and sweating. Intravenous solutions of hypertonic glucose are helpful in supporting the circulation, and therapy for shock is to be instituted if the shock syndrome intervenes. When cerebral excitement is prominent, small doses of sedatives may be needed. When the poisoning has advanced to the stage of central depression, stimulants such as caffeine and ephedrine may be required. Epinephrine is the drug of choice in treatment of allergic manifestations and it usually controls urticaria and angioneurotic edema without difficulty. On the other hand, asthma due to acetylsalicylic acid may at times prove most refractory to therapy.

Clinical Uses of the Salicylates

There are many local and systemic uses of the salicylates. Several of these are dictated by tradition and empirical results rather than by a clear understanding of the mechanism of therapeutic relief. The majority of the properties attributed to salicylates by the laity and for which they are widely used have no existence in fact.

Local Uses. *Salicylic acid* is employed only externally. It is incorporated in a concentration of two to 10 per cent in lotions, collodion and ointments as a keratolytic agent. A familiar example is the combination of salicylic acid with benzoic acid (Whitfield's ointment), often prescribed for epidermophytosis. A particularly beneficial powder for ringworm of the feet has been described by Prehn (1938) and consists of five parts of salicylic acid, two parts of menthol, eight parts of camphor, 50 parts of boric acid and 35 parts of starch. The acid is also employed as a *wart* and *corn* remover (10 to 20 per cent in collodion) and in chronic skin diseases such as eczema. It is sometimes prescribed in talc (two to four per cent) against hyperhidrosis. Salicylic acid should not be used as a food preservative.

Methyl salicylate is reserved for external use as a counterirritant. It is employed for painful muscles or joints and can be diluted with two parts of olive oil or incorporated in an ointment. Some cutaneous absorption may occur but any benefit is due entirely to the local actions. Methyl salicylate is also used as a flavoring agent.

Phenyl salicylate is used only as an enteric coating material for capsules or tablets, when one desires to protect drugs from gastric secretions. The encapsulated material is released in the duodenum where the salol is hydrolyzed.

Sodium salicylate may be used for sclerosing varicose veins. Three to five cc of a 20 to 40 per cent sterile solution are injected.

Systemic Uses. *Antipyresis.* Antipyretic therapy is not as common today as it was formerly, and is reserved for those conditions in which fever in itself may be deleterious, or when the patient experiences considerable relief when the temperature is lowered. The tendency is to use baths and alcohol sponges rather than drugs. Little is known about the relationship between fever and immune processes, and the former may at times be a protective physiological mechanism. Again, the course of the patient's illness may be obscured by the relief of symptoms and the reduction of fever consequent upon the use of salicylates.

The antipyretic dose of salicylates is from 0.3 to 1.0 gram given orally as tablets or capsules every three or four hours. Better effects are obtained in cyclic fevers and when the drug is given to coincide with the expected defervescence. The antipyretic action of the salicylates is nonspecific and does not influence the course of the disease.

Analgesia. The salicylates are valuable for the *nonspecific relief* of certain types of pain arising from muscles, joints, and integumental structures, as for example, migraine, arthritis, dysmenorrhea, neuralgias, myalgias, etc. For this purpose salicylates are prescribed in the doses and manner outlined for antipyresis. A combination of drugs selected from different chemical groups is often more effective than a single substance, and represents one of the few valid uses of drug combinations. Thus salicylates are often combined with a barbiturate or codeine, together with either a pyrazolon or paraminophenol derivative. The combination should be ordered by the physician and in such relative doses as he deems necessary for the particular patient and illness. The use of proprietary preparations can only be deplored.

Use of Salicylates in "Cold," and "Grippe." The salicylates do not influence the course of the common cold or upper respiratory infections, and lack specific action in these disorders. They may make the patient more comfortable by reducing the temperature and relieving headache and muscle aching. If the symptomatic improvement tempts the individual to be ambulatory during his infection, the drug has done more harm than good. The use of gargles containing acetylsalicylic acid has no benefit other than those obtainable from solutions of sodium chloride.

Use of Salicylates in Gout. The salicylates are capable of relieving the acute attacks of gout when given in fairly large and repeated doses. They are somewhat inferior to cinchophen, especially for the therapy of chronic gout and the prevention of acute exacerbations. The probable mechanism of action and the results obtained are more fully discussed in connection with cinchophen (page 237).

Use of Salicylates in Acute Rheumatic Fever. Either sodium salicylate or acetylsalicylic acid may be used. The amount prescribed is much larger than that employed for any other purpose. A dose of 1.0 to 1.3 grams is given hourly until symptoms of salicylism ensue or until the desired clinical effects are obtained. This usually requires eight to 10 doses—a total of eight to 13 grams or more of salicylate. Acetylsalicylic acid is effective in a somewhat lower total dosage than sodium salicylate. After early toxic effects develop, such as ringing in the ears and dizziness, medication is omitted for 12 hours, and is then resumed at the lower dose level of 1.0 gram every four or five hours during the day. This is continued until all signs of active infection have been absent for a week or 10 days.

As stated previously, the mechanism of action is unknown. It is difficult to accept the conclusion that relief is entirely due to analgesia and antipyresis. Morphine, for example, relieves pain but does not affect the inflammation of the joints.

Despite the fact that migrating polyarthritis responds in a remarkable manner, the course of the disease is not shortened and complications are unchanged by salicylates. Usually within 24 to 36 hours there is apparent improvement or complete relief of pain, swelling, immobility, local heat, and redness of the joints. The fever and pulse rate are lowered and the patient feels greatly benefited. Complete relief is obtained in over 80 per cent of acute cases and failure occurs in only one to two per cent of patients. These dramatic changes do not occur in arthritis of streptococcal, gonococcal, or other origin. Therefore, the failure to obtain relief in suspected rheumatic polyarthritis is fairly good presumptive evidence that the diagnosis is faulty. At least, when rapid and characteristic benefit occurs, the diagnosis of acute rheumatic fever is strengthened.

No further joint involvement occurs during salicylate therapy. Cessation of medication, however, may result in recrudescence of symptoms. The elevated white blood cell count is also reduced by salicylates, and if the leukocytes remain at a normal level when medication is stopped, this is strong evidence that the infection has disappeared.

The management of the patient does not change because of salicylate medication, and absolute rest in bed, maintenance of fluids and nutrition, and careful attention to the heart must not be neglected merely because the patient is symptomatically improved. Cardiac complications in particular should be watched for, because salicylates do not in any way prevent their occurrence.

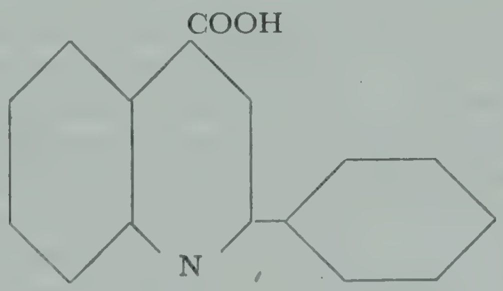
The many aspects of the therapy of rheumatic fever have been reviewed authoritatively by Cecil (1940).

Use of Salicylates in Ocular Inflammation. In cases of acute intra-ocular inflammation, the salicylates may give marked relief from pain and produce a diminution of inflammatory changes, such as congestion and swelling (Gifford, 1939). The mechanism of this action is unknown. Sodium salicylate or acetylsalicylic acid may be given in doses as large as those employed in acute rheumatic fever.

CINCHOPHEN

Cinchophen was synthesized in 1887 by Doebner and Gieseke, and was introduced into medicine under the trade name of *Atophan* by Nicolaier and Dohrn in 1908. As the term atophan suggests, the drug was proposed for the treatment of gout, and this still remains its chief use.

Chemistry and Preparations. Cinchophen is 2-phenylquinoline-4-carboxylic acid and has the following structural formula:



Cinchophen

Cinchophen is a yellowish-white bitter powder which is insoluble in water. It is official in the N.F. and in the B.P.

Pharmacological Actions. In nearly all its major actions, cinchophen resembles the salicylates. Its *antipyretic* and *analgesic* actions are similar to those of salicyl compounds, both in degree and mechanism. The *uricosuric* effect of cinchophen has already been discussed at length (page 227) and is more pronounced and more rapid than that of salicylates. A single dose exerts its greatest influence within three hours and is practically without further effect after nine hours. The ability of cinchophen to increase bile flow is said to be more pronounced than that of the salicylates. The *renal effects* are the same as for the salicyl drugs. The *antirheumatic* action of cinchophen has permitted its successful use in acute rheumatic fever.

Absorption, Fate and Excretion. Cinchophen is absorbed adequately from the intestinal tract. After cinchophen medication, the urine may assume a reddish color and turn green on the addition of acid, due to the presence in the urine of oxidation products, the exact chemical nature of which is disputed. Quantitative data on the excretion of cinchophen are lacking.

Doses and Administration. Cinchophen is always given orally, usually in capsules or tablets. The average analgesic or antipyretic dose is the same as that of sodium salicylate, namely, 0.3 to 1.0 gram every three or four hours. In rheumatic fever, the doses and intervals are the same as for the salicylates. The usual amount in acute gout is 0.5 gram every two hours for six or more doses.

Cinchophen, partly due to its acidity, causes a sensation of burning in the throat and irritation of the stomach. Experimentally, cinchophen has been employed in animals to produce gastric ulcers, and peptic ulcer has been recorded in human beings from the use of cinchophen (Block and Rosenberg, 1934; MacBryde, 1940). The gastric distress can be ameliorated by giving sodium bicarbonate, but the alkali is not to be mixed with the cinchophen. An ample amount of water should also be taken. When cinchophen is employed in patients with gout or with a tendency to form urate calculi, the combined use of water and sodium bicarbonate will prevent the precipitation of urate which is prone to occur in concentrated acid urines. Enough bicarbonate should be prescribed to make the urine alkaline, usually 15 grams on the first day of cinchophen medication when uric acid excretion is highest, and five to 10 grams on subsequent days. Potassium or sodium acetate or citrate may be used instead of sodium bicarbonate, but these do not ameliorate gastric irritation.

Toxicology. Before 1925, cinchophen was looked upon as a drug with approximately the same potentialities for poisoning as the salicylates. It causes all the symptoms of salicylism and produces skin lesions, angioneurotic edema and other allergic reactions similar to those from acetylsalicylic acid. Salicylism, however, does not occur quite so readily. In addition, cinchophen given to patients with cystitis may cause hematuria and pain in the bladder. Rarely, peptic ulcer may occur from the drug. The symptoms and treatment of acute poisoning by salicylates apply in all particulars to cinchophen.

Since 1925 an increasing number of cases of severe toxic reactions and fatalities from cinchophen have been reported. All of these have been due to a hepatotoxic effect of the drug. Up to 1936, 191 cases had been reported and 47 per cent were fatal. Other fatalities were reported subsequently (*see* Sugg, 1938; MacBryde, 1940). Probably hundreds of similar cases were unrecognized or unreported. It is true that the annual consumption of cinchophen in the United States alone was estimated at one time to be 90,000 pounds (White, 1931) and therefore the absolute incidence of liver damage is extremely low. Nevertheless, the serious nature of the lesion and the high mortality rate make it necessary that the physician give careful thought before using this drug. If cinchophen were an indispensable agent like morphine, there would be little question that its employment should continue despite the occasional untoward reaction.

The symptoms of liver involvement are much like those noted in delayed chloroform poisoning. Indeed, the initial symptoms may not be evident until the drug has been discontinued for days or weeks. Anorexia, nausea and vomiting are first noted and are soon followed by pruritus, icterus, fever, and hepatic tenderness and swelling. Stupor gradually develops and death may ensue after a few days or in a week or two. The capriciousness and unpredictability of cinchophen hepatitis are the most disturbing features about the drug. Toxicity is unrelated to dosage or to previous medication. The fact that a patient has taken cinchophen previously without ill effects is no guaranty that the next course of cinchophen will not cause jaundice and death. Large amounts may be taken for years without liver damage, and yet in other patients small amounts given for a few doses may prove fatal. Once symptoms have appeared, poisoning progresses despite discontinuance of medication. For this reason, Palmer and Woodall (1936) in their review of cinchophen poisoning conclude that "there is no safe way for the administration of cinchophen."

The nature of the liver injury is a toxic cirrhosis which may proceed to a fulminating yellow atrophy. The results of extensive animal experimentation have not elucidated the mechanism of this hepatotoxic action nor are they in accord with clinical experience. In man there appears to be a large and essential element of hypersusceptibility or idiosyncrasy which is not related to age, sex, allergy or previous use of the drug. It is possible that preexisting and clinically unrecognized liver damage may predispose to toxic reactions to cinchophen (Rawls and coworkers, 1939).

Inasmuch as the sensitivity of patients cannot be determined beforehand by any known test, the responsibility for the use of this drug rests upon the physician who elects to prescribe it. A major danger also exists in the lay use of proprietary drugs because more than 30 preparations have been placed on the market which are known to have contained cinchophen or its derivatives. In addition, at least 500 patented remedies have been advertised for the cure of rheumatic or uric acid disturbances, and probably a number of these included cinchophen (Hench, 1932). The present Federal control of the sale and distribution of cinchophen is to be commended.

The *treatment* of toxic cirrhosis due to cinchophen is symptomatic and supportive, and similar to that for chloroform and carbon tetrachloride injury to the liver. Surgical measures in patients with cinchophen hepatitis should be strictly avoided because the outcome is nearly always fatal. Intravenous administration of saline and glucose solutions is an important means of replacing the fluid and electrolyte lost incident to vomiting and diarrhea, and of giving nourishment, preventing acidosis and aiding the liver through replenishment of its glycogen stores. The diet should be high in carbohydrates and calcium and low in fats.

Therapeutic Uses. Cinchophen has no local uses analogous to those of the salicylates. The drug is employed for its systemic effects in the same manner and for the same conditions as are the salicylate compounds. Thus it is given for *analgesia* and *antipyresis,* but the possibility of toxic cirrhosis should certainly favor the selection of other agents for these purposes. Cinchophen is also effective in *acute rheumatic fever* where it compares favorably with the salicylates. Again, however, the choice of medication should be the salicylate drugs because they do not cause fatalities from liver injury.

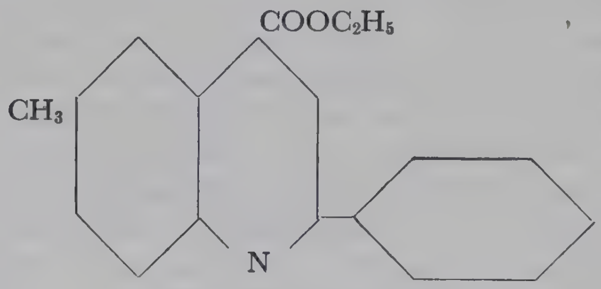
The disease for which cinchophen has been retained by some physicians, despite its known propensity as a hepatotoxic agent, is *gout.* Even here, however, there is no unanimity of opinion. Some clinicians, who treat many cases, claim to obtain satisfactory results from salicylates or colchicine, and therefore no longer use cinchophen. Others believe that in *chronic gout,* at least, there is no drug that can equal cinchophen for controlling the disease and preventing its progress to gouty nephritis and cerebral vascular or coronary complications. These complications may cause the death of the patient with chronic gout five years before his time, statistically speaking. Those who still use cinchophen believe the danger of the disease is greater than that of the drug (Hench, 1937). If cinchophen is employed for chronic gout, it may be given in the dose of 0.5 to 1.5 grams three times daily for three consecutive days each week. This is continued for months or even years. The drug should be given only under close medical supervision, and should be discontinued at the first sign of intoxication. As stated previously, this does not insure against serious or fatal poisoning. In the *acute attack of gout,* cinchophen gives no better results than can be obtained with salicylates or colchicine, and the latter drugs should be employed. If cinchophen is used, the dose is 0.5 gram every two or three hours for five or six doses.

In gout, the concentration of uric acid is high in the blood and low in the urine. The relation of gout to a faulty uric acid metabolism is generally agreed upon. The details of this association are so poorly understood, however, that the etiotropic effects of uricosuric drugs cannot be taken for granted. At least some of the relief obtained is on an analgesic and not on a specific basis. It is doubtful whether cinchophen actually decreases the urate deposit in tophaceous lesions or hastens their resolution. Cinchophen may give relief without noticeably affecting uric acid metabolism, and may fail to afford respite from an acute attack despite an increased uric acid output. Colchicine, as will be noted later, is quite effective without altering the uric acid content of the urine or blood.

Other measures employed in the acute attack of gout are morphine at the height of the pain, abundant fluids, purine-free diet, and local protection of the involved joint by cotton swathing.

NEOCINCHOPHEN

Neocinchophen, U.S.P., (novatophan, tolysin) is the ethyl ester of 6-methyl-2-phenylquinoline-4-carboxylic acid. Its structural formula is as follows:



Neocinchophen

It is a light yellow crystalline powder which is tasteless, odorless and nearly insoluble in water.

Actions and Uses. In all its pharmacological actions, neocinchophen resembles cinchophen. It has the advantage of being almost non-irritating. Intestinal absorption, however, may be incomplete as a result of its limited solubility. It is apparently absorbed as such, and is excreted in the urine partly unchanged and partly as an oxidation product.

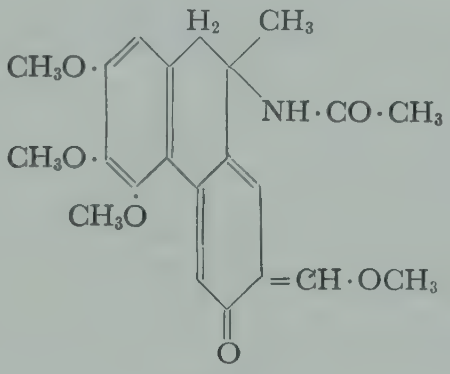
The clinical uses and dosages of neocinchophen do not differ from those of cinchophen itself. The question arises whether neocinchophen is as toxic as the parent compound. Experimental data on animals seem to indicate a higher margin of safety which appears to be due to the rather poor intestinal absorption of neocinchophen. Symptoms of salicylism do not occur as often as with cinchophen.

In man, the incidence of toxic cirrhosis of the liver following neocinchophen medication is difficult to determine because of inaccurate data on the extent to which this drug is used. An analysis of the seven cases of serious neocinchophen poisoning reported in the literature up to the middle of 1936 showed that five deaths occurred (Palmer and Woodall, 1936). The alleged greater safety of neocinchophen is still a moot point, and the burden of proof rests on those who make this claim.

COLCHICUM

Colchicum autumnale is the autumn crocus (meadow saffron) whose seeds and corm contain an alkaloid, *colchicine,* which is effective in the treatment of acute attacks of gout. It has no other therapeutic uses, although it is valuable experimentally for its effects on plant and animal cell division. The poisonous action of colchicum was known to Dioscorides but its use in gout dates from the sixteenth century.

Chemistry and Preparations. The structural formula of colchicine is as follows:



Colchicine

Colchicum seeds, the U.S.P. source of colchicine, contain about 0.5 per cent of the alkaloid. The preparations and doses used are *Colchicine,* U.S.P., 0.5 to 1.0 mgm; *Tincture of Colchicum Seed,* U.S.P., 1.0 to 2.0 cc (*Tincture of Colchicum,* B.P., 0.3 to 1.0 cc); *Strong Tincture of Colchicum Corm* (Wine of Colchicum Corm), N.F., 0.6 cc; *Dry Extract of Colchicum,* B.P., 0.015 to 0.060 gram; *Liquid Extract of Colchicum,* B.P., 0.12 to 0.3 cc.

Pharmacological Actions. *Gout.* Colchicum occasionally affords dramatic relief in acute gout. The drug has no effect on uric acid metabolism. It does not relieve other types of pain or inflammation and the mechanism of relief in gout is inexplicable.

White Blood Cells. In several species of animals, colchicine produces a temporary leukopenia which is soon replaced by a more lasting leukocytosis. This is sometimes due to a striking increase in the number of basophilic granulocytes. The site of action is apparently directly on the bone marrow.

Mitotic Arrest of Rapidly Dividing Cells. Colchicine, in proper concentrations, has the ability to arrest cell division in the metaphase and to cause bizarre mitotic figures (Dustin, 1934; Brues and Jackson, 1937). Larger doses may completely prevent cells from entering mitosis. This remarkable action of the drug holds *in vitro* and *in vivo* for normal cells, rapidly regenerating cells and for cancer cells, and has been employed to study the rate and characteristics of abnormal cell growth (Oughterson and coworkers, 1937), as well as the effects of carcinogenic agents and endocrine substances on these properties (Allen and coworkers, 1937). It has also been used to produce regression in certain types of experimental tumors. A number of colchicine derivatives have been found to act in a similar manner (Brues and Cohen, 1936), but the exact chemical grouping necessary for this property remains undetermined. The failure of the mitotic spindle to develop and function normally is thought to be the cause of the arrest of cell division (Ludford, 1936). That colchicine is not specific is indicated by the fact that sodium cacodylate produces similar nuclear abnormalities (Dustin, 1934).

Toxicity. Colchicine poisoning usually results from clinical overdosage. At one time colchicum was employed for criminal poisoning. An interesting but unexplained feature of the intoxication is the latent period of several hours or more between the administration of the drug and the onset of symptoms. This interval is not altered by dosage or route of administration. Evidence has been produced that colchicine must first be changed to a toxic oxidation product (oxydicolchicine).

Gastro-intestinal symptoms are the first to appear, probably as a result of the excretion of the drug by this channel. There is severe abdominal pain, nausea, vomiting and diarrhea. The diarrhea soon becomes profuse, watery and bloody due to a hemorrhagic gastro-enteritis. Considerable fluid, electrolyte and blood plasma are lost through the bowel, and in this respect the picture is similar to that of acute arsenic poisoning. Even when given by injection, colchicine causes gastro-intestinal irritation and burning of the throat and skin. Because of the extensive vascular damage, the shock syndrome occurs.

The kidney, another site of excretion of colchicine, is also injured and hematuria and oliguria follow. The pulse is rapid and weak and the patient greatly exhausted. Muscular depression is pronounced, an ascending paralysis of the nervous system develops, and death results from respiratory arrest usually within a day or two. Consciousness is present to the end, but terminal delirium or convulsions may appear.

Fatal Dose. This varies considerably. Fifteen cc of the tincture of colchicum seed, corresponding to six mgm of colchicine, have proved fatal but the patient may survive larger doses.

Treatment. In addition to gastric lavage, therapy should be directed very early against shock. The remaining measures are purely symptomatic and supportive. Atropine and morphine aid in relieving abdominal pain. Artificial respiration should be tried when paralysis begins to involve the cervical region of the spinal cord.

Clinical Uses. Colchicine is used in gout on an entirely empirical basis. Better results are obtained in the acute episodes and the drug should be used as early in the attack as possible. Many patients fail to respond to colchicine but some experience striking benefit. The pain, swelling and redness are relieved within a few hours and the attack is brought to an abrupt close. Some early gastro-intestinal side-actions, such as diarrhea, must be tolerated before the patient is benefited. Colchicine is practically valueless in chronic cases, and continued treatment with it does not appear to lessen the frequency of gouty episodes. Colchicine is usually given in tablet form in a dose of one mgm and repeated every two or three hours for four or five doses. If colchicine is available there is reason to prefer it because the wine and tincture are more uncertain in their effects, probably due to deterioration. Many patients experience gastric distress or diarrhea on the second day of treatment. If severe nausea, diarrhea or great weakness is experienced, medication should be stopped and other measures used. Also, the drug should not be continued after the pain has been relieved.

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CHAPTER 14

ANALGESICS AND ANTIPYRETICS

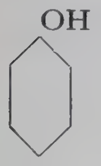
II. ACETANILID AND ACETOPHENETIDIN; AMINOPYRINE AND ANTIPYRINE

ACETANILID AND ACETOPHENETIDIN

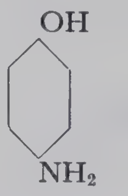
Acetanilid and acetophenetidin are known as "coal-tar" antipyretics. They are sometimes termed paraminophenol derivatives, although strictly speaking acetanilid cannot be classified in this way. These drugs are also called aniline derivatives, a designation too broad to be helpful. In the body, as will be noted later, it is likely that both acetophenetidin and acetanilid exert their typical action after being changed to paraminophenol.

Acetanilid was introduced into medicine as an antipyretic under the name of *antifebrine* by Cahn and Hepp in 1886. The early reports of serious poisoning from the drug prompted the search for less toxic compounds. *Paraminophenol* itself was tried in the belief that the body oxidized acetanilid to this compound. Toxicity was not lessened, however, and a number of chemical derivatives of paraminophenol were then tested. The most satisfactory of these was *acetophenetidin,* introduced under the trade name of *"phenacetine."* This compound and acetanilid are the only two which have survived the past 50 years of clinical trial, but the less toxic salicylates have overshadowed the use of these drugs both as analgesics and antipyretics. Acetanilid and acetophenetidin are common constituents of headache and "pain-killing" mixtures of secret composition, and most poisonings by this group of drugs result from the lay use of such patent medicines.

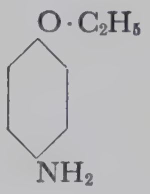
Chemistry and Relation of Chemical Structure to Action. The relationship between phenol, aniline and the drugs under discussion can be seen by an inspection of their structural formulas.



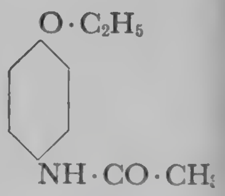
Phenol



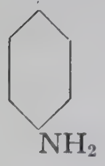
Paraminophenol



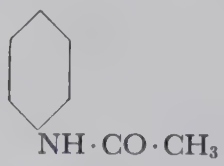
Phenetidin



Acetophenetidin



Aniline



Acetanilid

The *antipyretic action* of these compounds resides in the aniline structure, and aniline itself is antipyretic but its toxicity precludes its clinical use. Introduction of other radicals into the OH of paraminophenol and into the free amino group of aniline reduces toxicity without loss of antipyretic action. Best results are obtained when an alkyl group is substituted in the OH (ethyl in acetophenetidin) and an acid group in the NH_2 of aniline (acetyl in acetanilid and acetophenetidin).

It is believed that both acetanilid and acetophenetidin owe their therapeutic as well as their toxic actions to conversion in the body to paraminophenol. In the case of acetanilid, this requires the addition of an hydroxy group in the position para to the amino group. That this may occur in the body is suggested by the *in vitro* work of Michel, Bernheim and Bernheim (1937) whose study indicates that acetanilid is hydrolyzed by various tissues to acetic acid and aniline, and that aniline in the presence of tissue may be oxidized to p-aminophenol.

Pharmacological Actions. The two chief systemic actions of acetanilid and acetophenetidin are *antipyresis* and *analgesia.*

Antipyresis. This action does not differ from that described for the salicylates. Acetanilid and acetophenetidin act on the heat-regulating centers of the nervous system to bring about a greater dissipation of body heat through cutaneous vasodilatation. A measure of *tolerance* is said to develop to the antipyretic action in some patients.

Analgesia. The mechanism of obtundation of pain by acetanilid and acetophenetidin is similar to that described for the salicylates. The action is central, probably on the optic thalamus. The type of pain relieved is that which usually occurs in headache, and in many muscle, joint and peripheral nerve affections. Intense pain or that arising from smooth muscle spasm in hollow viscera is not alleviated. The nature of this limited analgesic action is not understood, but it is selective and the drugs are not central depressants as are the hypnotics. Acetophenetidin may raise somewhat the cutaneous threshold for touch, but this modality of sensation is not affected nearly to the same extent as is pain.

Absorption, Fate and Excretion. Acetanilid and acetophenetidin are quickly absorbed from the gastro-intestinal tract. In the body they are probably converted to paraminophenol and possibly to hydroxyphenylhydroxylamine. They are excreted rapidly by the kidney as conjugation products with glycuronic and sulfuric acids and can impart a dark amber or wine color to the urine, which may turn dark brown or black especially if it has been exposed for some time to the air. The urine may give a positive "indophenol" test as a result of the conjugated excretory substances.

Doses and Preparations. *Acetanilid,* U.S.P., and *Acetophenetidin,* U.S.P., B.P. (phenacetin), are white crystalline powders. They are always given orally, usually in powder, capsule or tablet form, being too insoluble to be prescribed in aqueous solution. If they are used in powder form, their taste is not objectionable. The average single dose of acetanilid for adults is 0.2 gram, and that of acetophenetidin 0.3 gram. If given in mixtures, the drugs should not be prescribed with antipyrine because liquefaction occurs.

Therapeutic Uses. The analgesic and antipyretic uses of these compounds are exactly the same as for the salicylates. In contrast to the salicylates, however, acetanilid and acetophenetidin are not employed for relief in gout or rheumatic fever because they lack an uricosuric action or any "specific" effect on the polyarthritis of acute rheumatic fever. In addition, they are considerably more toxic than the salicylates and cannot be used as continuously or in such large doses without risk of poisoning.

Analgesic Uses. In headache, migraine, dysmenorrhea, arthralgia, myalgia and similar disorders, a therapeutic dose of acetanilid or acetophenetidin may be given every three or four hours. Medication over a period of days is not advised unless there are intermittent periods during which analgesic drugs from other chemical groups are substituted. If ordinary doses are ineffective, larger amounts as a rule do not give relief.

As emphasized for the barbiturates and again for salicylates, a smoother and more efficient analgesic action may be obtained by prescribing a mixture of two or three analgesic chemicals. These should be selected from different classes of drugs and the dose of each reduced to one-half or less. This represents one of the few valid uses of drug combinations. The possibility of untoward reactions is also reduced because the toxic effects of the salicylates, pyrazolon and paraminophenol derivatives differ somewhat from each other. Often a barbiturate or codeine may be added to such a mixture, and caffeine is a frequent constituent of analgesic combinations prescribed for headache.

There is probably no other field in which commercial drug exploitation is so extensive as in the manufacture and over-the-counter sale of *headache nostrums.* Many of these preparations contain acetanilid, acetophenetidin and amidopyrine, all of which are capable of causing serious and even fatal intoxication. Salicylates are also commonly included. The names of these "patent" medicines usually give no indication as to the nature of their drug content. Their wide use by the laity cannot be too forcefully deplored and condemned.

Antipyretic Uses. The original use of acetanilid and acetophenetidin to reduce fever has been supplanted by their employment for relief of pain. The antipyretic dose has been stated previously. The indications and rationale for reducing body temperature are discussed in connection with the salicylates, and apply to these drugs also. It is perhaps best to give smaller doses at intervals of one or two hours than to prescribe the full dose every three or four hours.

Toxicology. Poisoning by acetanilid and acetophenetidin nearly always occurs from their medicinal misuse rather than from attempts at self-destruction. Most cases of intoxication have resulted from the ingestion of proprietary drug mixtures, usually headache powders. Poisoning may be acute or chronic, but the latter is the more frequent type and death may result from either. Acetanilid is definitely more toxic than acetophenetidin, perhaps because the latter is less soluble and is oxidized very slowly in the body to more toxic products. Considerable individual susceptibility is manifested to these drugs and the toxic dose for one patient may be harmless for another. The cause of this variation is unknown. Undoubtedly the nature of the disease for which the drugs are taken can add greatly to the untoward reactions caused by them. Most of the early reports of death from acetanilid were definitely due to overdosage because the potentialities for poisoning from the chemical were not at first appreciated.

Acute Poisoning. Symptoms. The most outstanding characteristic of acetanilid poisoning is *cyanosis.* Acetophenetidin causes this symptom much less frequently. The cyanosis is due to alterations of hemoglobin to *methemoglobin* and *sulfhemoglobin.* Many of the signs and symptoms of intoxication are a direct result of this change in blood pigment. The patient shows a bluish color of the skin, mucosa and finger nails and the altered pigment may be detectable on spectroscopic examination of the blood. This diagnostic test is not always positive because a higher concentration of methemoglobin is needed for detection by the usual laboratory spectroscope than is necessary to produce cyanosis and clinical symptoms. Therefore, the absence of the characteristic absorption bands for methemoglobin, upon examination of the blood of a patient suspected of acetanilid or acetophenetidin poisoning, does not necessarily exclude these chemicals as the cause. In severe cases of poisoning, the blood is often chocolate-colored due to its high content of methemoglobin.

The conversion of hemoglobin to methomoglobin and sulfhemoglobin occurs within the red blood cells and the latter are not injured as a rule. High concentrations of the drug, however, may occasionally result in actual destruction of the corpuscles. This is especially true for the related chemicals—aniline, nitrobenzene and phenylhydrazine. Acute intravascular hemolysis of a large number of red blood cells is a serious complication. The ensuing anemia may be profound and the red cell count may fall quickly to levels between one to two million per cubic mm. In addition to symptoms of anemia, renal function is seriously impaired and the urine contains albumin, casts, red blood cells and free methemoglobin. Oliguria or anuria may occur as it also does in cases of hemoglobinuria resulting from faulty blood transfusions. The blood contains free methemoglobin and cell membrane fragments. There is also leukocytosis and the blood smear in some respects is similar to that seen in the acute episodes of hemolytic jaundice or sickle cell anemia.

The mechanism of formation of methemoglobin and sulfhemoglobin by acetanilid and acetophenetidin is a matter of dispute. These drugs do not form the pigment when added to blood in a test tube. In the body, however, some change occurs which makes them capable of reacting with hemoglobin. Paraminophenol, for example, will promote methemoglobin formation *in vitro*. It is possible that paraminophenol or some oxidation product such as hydroxyphenylhydroxylamine is the substance responsible for the alteration in hemoglobin (Brownlee, 1939). There is also the possibility that some highly pigmented oxidation product of paraminophenol may be present in the blood and tissues and in itself cause or enhance the bluish color of the skin. Residual discoloration of both the blood and skin exists for some time after sulfhemoglobin and methemoglobin have disappeared and suggests such an explanation.

Methemoglobin is incapable of acting as a respiratory pigment. The reduction in the amount of hemoglobin available for oxygen transport results in *functional anemia*. Symptoms such as dyspnea, vertigo, weakness and anginal pain are prominent. In more severe cases, circulatory failure may ensue, the temperature is subnormal, prostration is marked, and respiration is rapid and shallow. The blood pressure is low and the pulse is rapid, weak and irregular. *Vascular collapse* is due not only to the relative anoxemia but also to a direct depressant action of high concentrations of acetanilid or acetophenetidin on the heart and blood vessels. Vascular dilatation and injury occur and set the stage for the *shock syndrome*.

Parenchymatous organs are also damaged, especially the liver, and the patient may develop jaundice. The *skin reactions* to toxic doses of these drugs may be a prominent feature and are noted especially with acetophenetidin. They are usually erythematous or urticarial in nature, but may be more serious and accompanied by mucosal lesions of the mouth. *Fever* may accompany the drug rash. Symptoms of *cinchonism* may occur but this is quite uncommon.

In the more severe grades of intoxication, *central nervous system stimulation*, excitement and delirium may be noted. This is followed by depression and stupor. Terminal asphyxial convulsions may develop. Death is usually preceded by a period of *collapse* and *coma*, and occurs suddenly or may be delayed for several days

The toxicity of acetanilid for the *heart* has received considerable attention. Ordinary therapeutic doses are not injurious to the normal heart but individuals with organic disease of cardiac or pulmonary origin are naturally more susceptible to the cardiovascular effects of the drug. Also, patients with anemia are more likely to develop symptoms of poisoning from the immoderate use of acetanilid or acetophenetidin. Indeed, in anemic individuals, the cyanosis may not be apparent despite a dangerously high concentration of methemoglobin. The repeated administration of these drugs to patients with anemia, or cardiac, pulmonary, renal or hepatic disease is definitely contraindicated.

The *fatal dose* of acetanilid cannot be stated accurately. As much as 4.0 to 8.0 grams has been taken without fatal results although smaller doses are claimed to have caused death. Animals survive proportionately much larger doses (Smith, 1940), and it is not clear whether a number of the reported human deaths attributed to the drug may not have been due in large part to underlying disease.

Chronic Poisoning. This may be extremely difficult to diagnose. Some chronically poisoned patients continue to take the drug for relief of the very symptoms caused by it. The cyanosis frequently present is often mistaken for a sign of congenital heart lesions or pulmonary disease. In addition to the suggestive skin and mucosal color, the patients complain of shortness of breath and severe weakness. There are also loss of weight, anorexia, digestive disturbances, and insomnia. Anemia is often prominent, and though it usually has the characteristics of the secondary type the blood occasionally may show elevated color and volume indices similar to those of primary anemias or acute hemolytic dyscrasias. There may also be a leukocytosis. Disturbances in the blood clotting mechanism may occur and metrorrhagia may be a presenting symptom of chronic acetanilid poisoning in women. The urine is sometimes brownish in color and gives the positive indophenol test. Rarely the blood may show methemoglobin or sulfhemoglobin, and its oxygen carrying capacity is then lower than is indicated by the hemoglobin content. This finding is of diagnostic importance, but many clinical laboratories are not equipped to do blood gas analyses. Of course, the diagnosis can be confirmed only by the patient's admission that the offending drug was ingested. This requires painstaking, diligent and often repeated questioning, and necessitates a knowledge of the names of the many proprietary nostrums which contain acetanilid or acetophenetidin.

Treatment. There is no specific therapy for *acute poisoning* by these drugs. If they have been recently ingested, gastric lavage should be performed and a solution of magnesium sulfate administered before the tube is withdrawn. Transfusion of blood may be needed to relieve the cyanosis and functional anemia in severe cases of intoxication. Artificial respiration may be required. Inhalation of oxygen and carbon dioxide is helpful. If an acute, severe hemolytic anemia occurs, blood transfusion is definitely indicated. This procedure also aids in protecting the kidneys against damage from the intravascular hemolysis. Sufficient alkali may also be given to make the urine alkaline in an attempt to prevent the further precipitation of free hemoglobin in the renal tubules with resulting obstruction to the flow of urine. Alkalis may also aid the reconversion of methemoglobin to ordinary oxyhemoglobin, as also does the administration of low doses of methylene blue (page 1032). The development of the shock syndrome calls for the measures outlined elsewhere.

In chronic poisoning, the drug must be completely withdrawn and supportive measures adopted to assist the patient back to health. These include the use of iron salts for the anemia. The blue color may not fade completely until several weeks after the cessation of the drug. The patient should be warned against the offending medicine. Rarely, a person may become habituated to acetanilid and continue to take it for a number of years. It has been reported that withdrawal symptoms of restlessness and excitement may appear for three or four days when medication is stopped (Payne, 1935), but it is extremely doubtful that true addiction occurs. The habit-forming properties of the analgesic-antipyretic drugs, however, cannot be denied.

ANILINE

Aniline, $C_6H_5NH_2$, is aminobenzene. It is purely of toxicological importance and has no medicinal uses. Aniline is a colorless oily liquid with a characteristic odor. Only after exposure to air does it acquire the brownish discoloration so often associated with it. Aniline produces the same general pharmacological effects as acetanilid but causes serious poisoning in amounts as small as 0.1 to 0.25 gram. It is of interest first because it provides the starting point for the manufacture of a number of drugs, and secondly because its wide use in industry ranks it as an important industrial hazard. Among other things, it is used in the synthesis of the aniline dyes, and in the manufacture of rubber and photographic materials. Poisoning is usually complicated by the fact that the aniline used industrially is impure and contains other toxic substances such as xylidine and toluidines. Intoxication may occur from inhalation of aniline vapors, from swallowing the chemical or from cutaneous absorption. The liquid can readily be absorbed through the intact skin and serious reactions have occurred from wearing apparel such as shoes newly dyed with chemicals containing aniline.

Symptoms of Acute Aniline Poisoning. The outstanding feature of aniline poisoning is methemoglobinemia. In the body, aniline is changed to the same intermediate oxidation products, paraminophenol and hydroxyphenylhydroxylamine, as is acetanilid and these are probably the cause of the methemoglobin formation. Cyanosis is so prominent a sign that workmen call aniline poisoning (and closely related nitrobenzene intoxication) the "blues." The symptoms and signs are essentially those described in detail for acetanilid. There is vertigo, headache, mental confusion, weakness and a desire to sleep. The skin and mucosa are blue and the pulse is fast and weak. The methemoglobinemia is more pronounced than in acetanilid intoxication and therefore poisoning is much more severe. The red blood cells are more apt to undergo intravascular hemolysis, with the resultant deleterious renal effects. The functional anemia due to methemoglobin is thus complicated by actual anemia.

Effects on the central nervous system are more prominent than in acetanilid poisoning and in the preliminary excitement stage the patient may appear to be inebriated. Later, there may be delirium followed by stupor and coma. Aniline is more toxic to the heart than is acetanilid, and cardiac collapse is more frequent. The action on the blood vessels is also more marked, and shock therefore is often present. If the patient survives sufficiently long, jaundice develops and blood cells and hematoporphyrin may appear in the urine. The liver and kidneys are likewise more severely damaged by aniline than by acetanilid. Death usually occurs within the first 24 hours from heart failure rather than from respiratory paralysis.

The *fatal dose* of aniline for human beings is difficult to state. Recovery has followed the swallowing of 75 cc, and death has resulted from one-third this amount. Again, as was stated, 0.25 cc may cause alarming symptoms.

Treatment. If aniline vapors have been inhaled, the victim should be removed immediately to the fresh air. Gastric lavage should be performed without delay if aniline was swallowed. When aniline has been spilled on the skin, it should be washed off promptly with copious amounts of water; but, if available, ether or alcohol is preferable to water because aniline is very soluble in these reagents. Treatment is the same as that outlined for acetanilid, with special emphasis on shock therapy, support to the cardiovascular system, and correction of the acute anemia with blood transfusion if necessary.

Chronic Aniline Poisoning. This occurs from repeated exposure to aniline in industry. Anemia is often marked and the usual train of symptoms from it are prominent. There is loss of appetite and weight, and cutaneous lesions are commonly noted. These are eczematoid in character and may become secondarily infected due to the poor health of the patient. Bladder symptoms are noted and consist of painful urination, frequency and urgency. The urine may be colored a dark brown due to the presence of conjugation products of paraminophenol. A high incidence of papilloma of the bladder occurs in workers in aniline industries, and this fact has been the subject of considerable investigation. These tumors apparently also occur from nitrobenzene and are thought by some to be due to oxidation products excreted in the urine which are irritant to the bladder even in high dilution. *Treatment* is purely symptomatic and removal of the patient from contact with the offending chemical is essential. Recovery may be slow. The bladder tumors may prove fatal.

NITROBENZENE

This chemical, $C_6H_5NO_2$, is a yellow, oily fluid which has the odor of oil of bitter almonds—benzaldehyde. It is important purely from a toxicological standpoint and has no uses in medicine. Aniline is obtained chemically from the reduction of nitrobenzene and the two chemicals are used similarly in many industrial processes. In addition, nitrobenzene, because of its pleasant odor, is employed as an artificial flavoring agent in foods, perfumes, soaps, etc. It is quite volatile and the vapors are more toxic than the liquid itself.

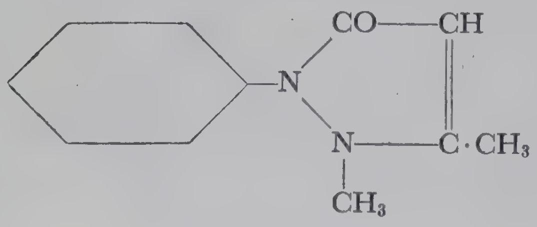
Poisoning. Nitrobenzene resembles aniline in being highly toxic to the blood and heart, but in addition it is a strong central nervous system depressant. Stimulation, however, may precede this depression. When nitrobenzene is swallowed, symptoms are often delayed for several hours. They then appear rather suddenly and in severe form. Inhalation of the vapors, on the other hand, promptly gives rise to marked effects. In either case, the patient acts as if he were inebriated. Headache, dizziness, nausea and vomiting, depressed respiration and visual disturbances are noted, and stupor and coma then follow. Death results from respiratory arrest. The blood changes are like those produced by aniline and the cyanosis is intense. It is claimed that both methemoglobin and nitrobenzene-hemoglobin are present. The blood is chocolate colored and acute hemolysis of red blood cells is not infrequent. The dark urine has the diagnostic odor of oil of bitter almonds, and this feature also characterizes the vomitus. *Treatment* is the same as for aniline poisoning.

Chronic intoxication results from repeated industrial exposure to nitrobenzene. It is characterized by cyanosis, visual disturbances, anemia, cachexia, peripheral neuritis and dysuria due to bladder irritation. Benign and malignant bladder papillomata apparently occur as in chronic aniline poisoning. *Treatment* is purely symptomatic and resembles that for chronic aniline poisoning.

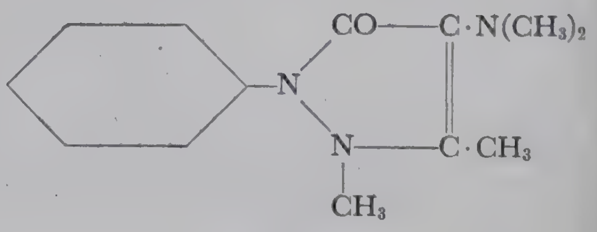
AMINOPYRINE AND ANTIPYRINE (PYRAZOLON DERIVATIVES)

Antipyrine (phenazone) was introduced into medicine in 1884. A few years later, a closely related compound, *aminopyrine* (amidopyrine), was synthesized and used clinically. Both antipyrine and aminopyrine were originally employed for antipyresis, but are now more often prescribed for analgesia. They share the general pharmacological properties of the salicylates and the paraminophenol derivatives, but differ somewhat in the type of poisoning they produce. This is especially true of aminopyrine which can cause severe and often fatal agranulocytic angina. For this reason, the clinical use of aminopyrine has been sharply curtailed. Antipyrine lost favor as the salicylates became more prominent, and it is rather infrequently prescribed today.

Chemistry. Both antipyrine and aminopyrine are phenyl-pyrazolon derivatives, aminopyrine being the dimethyl amino derivative of antipyrine. Their structural formulas are as follows:



Antipyrine



Aminopyrine

Pharmacological Actions. The two main systemic actions of aminopyrine and antipyrine are *analgesia* and *antipyresis*. In this respect they resemble the salicylates, acetanilid and acetophenetidin. In addition, antipyrine has some mild local anesthetic and antiseptic properties. Neither antipyrine nor aminopyrine shares the uricosuric action of the salicylates and cinchophen, but aminopyrine has the same antirheumatic effects. It can therefore be used in acute rheumatic fever. Other actions of these drugs are reserved for discussion in the section on poisoning.

Local Actions of Antipyrine. Antipyrine shares the local antiseptic property of the salicylates but the action is too weak to be of medicinal value. This drug is also a mild local anesthetic and was formerly used for anesthesia of the mucous membranes of the throat.

Analgesia and Antipyresis. The mechanism of antipyresis and analgesia produced by antipyrine and aminopyrine is similar to that of the salicylates. In equivalent doses, aminopyrine is more effective than antipyrine. Traditionally, aminopyrine has been used for analgesia and antipyrine for reducing fever, but there is no sound reason for this distinction. The analgesia may be enhanced if a combination of several drugs from different chemical groups is prescribed, as suggested under the salicylates.

Doses and Preparations. *Aminopyrine* (Amidopyrine) and *Antipyrine* (Phenazone) are official in the U.S.P. and B.P. Both drugs are white crystalline, odorless powders. The average dose of either aminopyrine or antipyrine for adults is from 0.3 to 0.6 gram, and this may be repeated at intervals of four hours. Although both compounds are soluble in water (antipyrine, 1:1, aminopyrine, 1:18), they are nearly always given orally in tablet or capsule form. Antipyrine liquefies when combined with acetanilid or acetophenetidin. *Melubrin* (N.N.R.) is another pyrazolon derivative which has not gained wide favor in the United States. It is closely allied to antipyrine which it resembles in pharmacological properties and therapeutic uses.

Absorption, Fate and Excretion. Both drugs are absorbed rapidly from the intestinal tract. There is little information on the fate of aminopyrine but it is probably similar to that of antipyrine which may be excreted in the urine unchanged or as oxidation products in conjugation with sulfuric and glycuronic acids. The urine may become blood-red in color after antipyrine and appear green in reflected light, but this is seen only after large doses.

Therapeutic Uses. These drugs are employed for *analgesia* and *antipyresis* in a manner exactly similar to the use of salicylates and paraminophenol derivatives. The action of aminopyrine is slower in onset but more enduring than that of antipyrine. In *rheumatic fever*, aminopyrine has been found to be as effective as the salicylates or cinchophen. The dose is much smaller than for the salicylates. For the first day of medication, 0.3 gram of aminopyrine is given every four hours for five doses (1.5 gram total dose). On subsequent days this can be reduced to 1.0 gram or less per day. The drug does not cause gastric distress as do the salicylates, and thus will not confuse the interpretation of abdominal symptoms due to early cardiac failure or overdigitalization. Despite these advantages and regardless of the fact that no serious untoward reactions have been reported from the use of aminopyrine in rheumatic fever, this drug should not be employed because of the danger of agranulocytosis. This is especially true because the salicylates are effective in acute rheumatic fever.

Toxicology. Poisoning from antipyrine and aminopyrine resembles that from acetophenetidin and acetanilid with the important exception that methemoglobinemia and cyanosis seldom occur. Large doses of antipyrine may occasionally cause alterations of hemoglobin but aminopyrine apparently does not affect the red blood cells. The effects on the central nervous system are more prominent with aminopyrine. In animals, stimulation sufficient to cause convulsions is produced, but this is rarely seen in human poisoning. Skin eruptions are more prone to occur after antipyrine, small doses of which may cause in certain patients a skin reaction similar to that seen with phenolphthalein. This consists of macular patches which are round or oval and vary in size from a few millimeters to several centimeters. They are pink or dark purple in color, last for months after the drug has been stopped, fade slowly, and leave pigmented areas which may flare up if the medicine is again taken. Aminopyrine is more likely to cause herpes labialis and angioneurotic edema in sensitive patients. The further details of the symptoms of poisoning may be found under acetanilid. The *treatment* is the same as for poisoning by the latter drug. If convulsions occur which are not terminal or asphyxial in character, they may be controlled by injection of a soluble short-acting barbiturate.

Aminopyrine Agranulocytosis. There are a number of drugs which are capable of producing severe and often fatal agranulocytosis. Among these are the arsenobenzenes, gold salts, dinitrophenol, benzol and sulfanilamide. Aminopyrine, however, occupies a peculiar position in this group because all the other chemicals can also produce disturbances of the red blood cells or platelets. Thus sulfanilamide causes acute hemolytic anemia; gold produces thrombopenic purpura; and benzol, dinitrophenol and arsenobenzenes may produce aplastic anemia and thrombopenia (Witts, 1936; Kracke, 1938; Fitz-Hugh, 1938). Aminopyrine can cause true agranulocytic angina in the sense that there is a marked leukopenia with an almost total absence of granulocytes, a maturation arrest of granulocytes at the stem stage in the bone marrow and no alterations in red blood corpuscles or platelets. This is the only drug of the analgesic-antipyretic or sedative-hypnotic group which is definitely known to cause the agranulocytic syndrome. The white cell count may be as low as 100 cells per cubic mm, the cells consisting entirely of lymphocytes. Fever, malaise, and ulcerations of the throat and other mucous membranes are often prominent. This syndrome, now known as agranulocytic angina, was first described by Schultz in 1922.

When the reports of aminopyrine as a cause of granulocytopenia first appeared in the early 1930's, it was not entirely clear whether aminopyrine or other drugs used in combination with it, such as the barbiturates, were responsible for the disorder. This point has been definitely settled and there is now no doubt that aminopyrine is the causative agent. The barbiturates definitely do not cause agranulocytic angina.

The *evidence for the causative rôle of aminopyrine* in agranulocytic angina has not always been dependable. In some cases at least, there was reason to suppose that the patient may have had the early symptoms of the disease and then taken aminopyrine for relief. A sufficient number of reports are now available, however, clearly to implicate aminopyrine as the causative agent. Indeed, there are some workers who are inclined to believe that aminopyrine is the sole cause of the disease. In certain individuals who have recovered from an agranulocytic attack it is possible to demonstrate an extreme sensitivity to the drug, because the ingestion of a small amount of aminopyrine results in the return of the characteristic blood picture and symptoms (Figure 22).

That there must be some large and determining element of *individual* *hypersusceptibility* in aminopyrine agranulocytosis is indicated by the low incidence of this bone marrow dyscrasia in comparison with the wide use of the drug. On the other hand, it is true that many cases have not been reported or have been unrecognized. What determines this hypersusceptibility is unknown. It is unrelated to sex, dose or previous use of the drug. Skin tests of the scratch, intradermal, patch or passive transfer type have yielded negative results. Dameshek and Colmes (1936), however, have demonstrated that when the drug is first incubated with the blood serum of the patient and the mixture injected intradermally, positive skin reactions may be obtained and are often accompanied by all the clinical and hematological features of agranulocytic angina (Figure 105). This suggests that a linkage between serum and drug may be essential for aminopyrine sensitivity. This observation is supported by the work of Landsteiner and Van der Scheer (1933) who found that the new antigenic property of substances formed by proteins linked to single chemicals was related to the non-protein part of the combination in regard to specificity. A typical blood response obtained by Dameshek and Colmes is presented in Figure 22. This illustrates the comparable effects of a large oral dose (0.6 gram) and a minute intradermal dose (10 mgm) of aminopyrine in a sensitive individual, and also clearly shows that skin testing is not without danger.

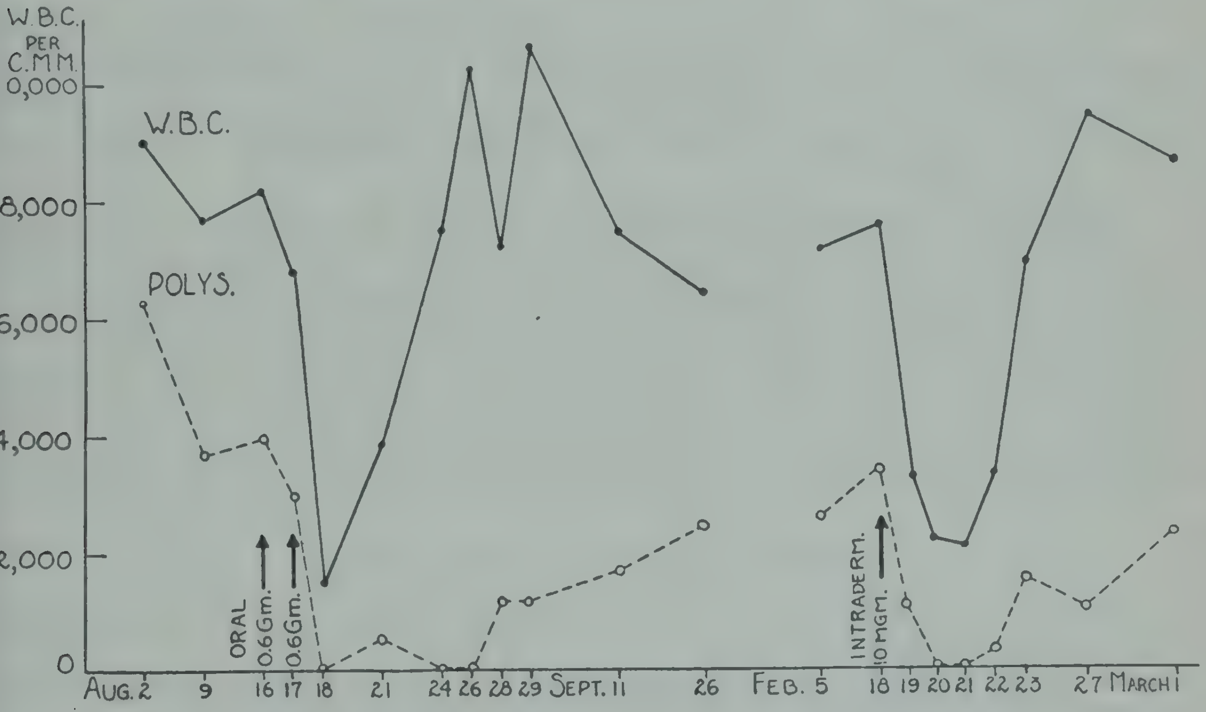


Figure 22. *Aminopyrine agranulocytosis.*

The patient was a woman, aged 49, who had had two previous attacks of agranulocytosis, at least one of which was due to aminopyrine. During a period of controlled observation, the patient ingested aminopyrine. First dose was taken at 7:00 P.M., Aug. 16th. Within 90 minutes severe headache, nausea, marked flushing of the face, malaise, weakness and joint pains were experienced. Second dose was taken on the following morning, and fever developed. Aug. 24th: Severe symptoms continued and ulcers were noted on the tongue and lips. Observe that the polymorphonuclear leukocyte count was only one per cent and that symptoms are related to agranulocytosis rather than to leukopenia. Patient did not feel better until Sept. 11th, when 25 per cent polymorphonuclear cells were present.

Scratch and intradermal tests with a five per cent solution of aminopyrine in distilled water were negative; but a positive reaction was obtained from a drug solution allowed to incubate with blood serum for several days before injection. The total amount of aminopyrine injected intradermally did not exceed 10 mgm, but the sequence of events which followed the oral ingestion of the drug was repeated. (After Dameshek and Colmes, 1936. Courtesy of the *Journal of Clinical Investigation.*)

The *mechanism of aminopyrine agranulocytosis* is unsettled. Animal experimentation has thus far not yielded a satisfactory answer. It is apparent that in certain sensitive individuals the drug can cause a maturation arrest of granulocytes in the bone marrow, and in such persons a minute amount may initiate the disease. Inasmuch as there is no certain or safe method of determining beforehand which patient will respond with agranulocytosis to aminopyrine, the question arises whether the drug should be used. It has been estimated that 30 million prescriptions alone were issued for this drug in the United States during the year 1934. When one adds to this the large "over-the-counter" sale of the chemical and of nostrums containing it, it can readily be appreciated that sensitivity is rare, because agranulocytosis is an uncommon disease. When the latter occurs, however, it is very serious and the mortality is high. For this reason and because aminopyrine is not indispensable, it is suggested that this drug not be used. As is the case with cinchophen, there is no "safe method" of administering the drug. The numerous warnings in the medical literature against aminopyrine have reduced considerably the prescribing of this drug. Whether the decline in agranulocytosis noted since 1933 is due to restriction in the use of aminopyrine is not known. It is instructive to note, however, that agranulocytic angina is unknown in Denmark where the medical profession has been induced to refrain from prescribing the drug.

The measures used in the *treatment* of agranulocytic angina are described elsewhere (page 1147). The patient should be warned against taking the drug, and told that there are numerous drug preparations and nostrums on the market which contain aminopyrine. A list of these drugs is presented by Hunter (1935) and Beckman (1938).

Many drugs containing aminopyrine are widely advertised for the relief of headache, dysmenorrhea and similar ailments, and are often dispensed by dentists for the relief of pain. It is interesting to note that a large number of the cases of aminopyrine agranulocytosis have occurred in nurses, technicians, physicians, and members of physicians' families. This is explained on the ground that samples of medicines containing aminopyrine sent to physicians by drug houses are readily accessible to these persons. The present control of the distribution and sale of aminopyrine by the Federal Food and Drug Administration is to be commended.

ACETANILID AND ACETOPHENETIDIN

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SECTION III

CENTRAL NERVOUS SYSTEM STIMULANTS

The central nervous system stimulants comprise a group of drugs which have in common the property of increasing the activity of various portions of the central nervous system. They differ markedly, however, both with respect to the locus and mechanism of this action.

Although the central nervous system stimulants are sometimes dramatic in their pharmacological effects, they are relatively unimportant from a therapeutic point of view. It is not possible to stimulate the nervous system over a long period of time, for heightened nervous activity is followed by depression, proportional in degree to the intensity and duration of the stimulation. Consequently, therapeutic excitation of the central nervous system is usually of brief duration and is reserved for emergencies characterized by severe central depression.

Another factor which limits the usefulness of the central stimulants is the multiplicity of their actions and the character of their side-effects. In this respect they are in marked contrast to the central depressant drugs which for the most part have a selective action on the nervous system. For example, caffeine not only stimulates the nervous system but also has a marked action on the heart, blood vessels and kidneys. Again, atropine and ephedrine stimulate the central nervous system but at the same time affect peripheral autonomic structures.

In this chapter, discussion will be limited to those drugs which have central stimulation as their predominant action, namely strychnine, picrotoxin, caffeine and related xanthines, coramine, metrazol and camphor. In addition to these agents, there is a large group of drugs whose property of central stimulation may be considered as secondary but important. These compounds include atropine, ephedrine, benzedrine, cocaine, nicotine, lobeline, carbon dioxide, cyanide, apomorphine, and emetine.

Finally, there are many drugs which, in toxic doses, temporarily stimulate the central nervous system. Compounds of this type are phenol, santonin, salicylates, local anesthetics, ergotoxine, etc. The central actions are described under the toxicology of these agents.

Whereas the number of drugs causing central excitation is large, the number employed clinically for this purpose is limited. Those which have special therapeutic value are the *respiratory* stimulants. In addition, central stimulants which act on the *vasomotor* or *vomiting* centers in the medulla have some usefulness. Lastly, there is a group of compounds known as *analeptics* which are employed to lessen narcosis. In some instances a single drug possesses several or all of the actions enumerated.

Although the therapeutic applications of the central stimulants are largely limited to their effects on the medulla, this is not the only site of action, for all portions of the cerebrospinal axis are affected by sufficiently large doses of the compounds.

Respiratory Stimulation. There are several physiological mechanisms by which stimulation of respiration can be accomplished. These are as follows: (1) the respiratory center can be stimulated directly either by drugs or by changes in the pH of the blood; (2) it responds readily to sensory impulses arising from the chemoreceptors of the carotid body; (3) the center is sensitive to afferent impulses, especially pain, coming from various parts of the body; (4) it also responds to the control exerted by the higher centers. The drugs which affect respiration act by one or more of these mechanisms. For example, caffeine stimulates the medulla directly. The locus of action of coramine, on the other hand, is on the carotid body. Reflex sensory stimulation of the medulla may be produced by local irritation resulting from the inhalation of ammonia or the subcutaneous injection of camphor, ether or alcohol. Ephedrine can stimulate respiration indirectly by lessening the degree of depression of the higher centers. Finally, a drug such as strychnine directly sensitizes the medulla to incoming stimuli and at the same time the analeptic action of the drug increases the number of effective impulses arising from other parts of the nervous system.

Vasomotor Stimulation. There are no drugs available which have a selective excitatory action on the vasomotor center but this portion of the medulla often shares in the general medullary stimulation produced by the respiratory stimulants and analeptics.

Stimulation of the Emetic Center. There are a few drugs which apparently have a selective action on the medullary vomiting center. These occasionally have some therapeutic application in the treatment of poisoning. The best example is apomorphine.

CHAPTER 15

STRYCHNINE AND PICROTOXIN

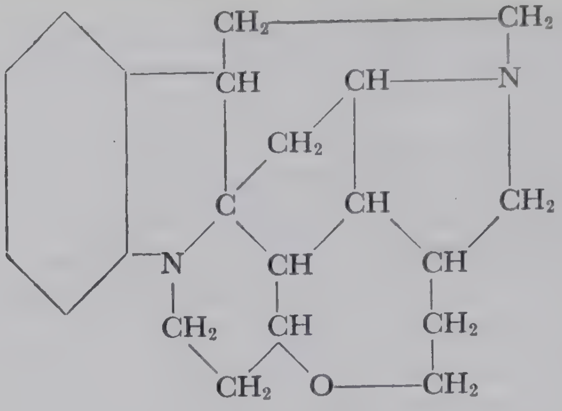
STRYCHNINE

Source. Strychnine is the principal alkaloid present in *Nux vomica,* the seeds of a tree native to India, *Strychnos nux vomica.* Nux vomica signifies "emetic nut." The origin of this name is puzzling, for strychnine is not emetic. It may have arisen through confusion with a nut of similar shape used by the Arabians for production of vomiting.

Nux vomica was introduced into Germany in the sixteenth century as a poison for rats and other animal pests. Its use as a rat poison persists to this day, and as an ingredient of "rat biscuits" strychnine is a source of accidental poisoning of children. Strychnine was first employed in medicine in 1540 but it did not gain wide usage until two hundred years later.

In addition to strychnine, the alkaloid *brucine* is found in nux vomica. Brucine, which is closely related to strychnine chemically, is much less active pharmacologically, and therefore the effects of extract of nux vomica are mainly due to strychnine.

Chemistry. Strychnine is an alkaloid of high molecular weight. It has the empirical formula $C_{21}H_{22}O_2N_2$ and the following probable structural formula (Achmatowicz and Robinson, 1938):



Strychnine

Pharmacological Actions

Central Nervous System. The outstanding action of strychnine is a stimulation of the central nervous system. All portions of the cerebrospinal axis are affected, but the predominant responses are referable to the functional changes produced in the spinal cord.

Spinal Cord. The action of strychnine on the spinal cord has been carefully studied and accurately localized. However, the exact mechanism by which the drug produces its characteristic effects is not fully understood. Strychnine in low dosage greatly increases the reflex excitability of the spinal cord. The result is that skeletal muscle responds in a coordinated but exaggerated manner. If the dose of strychnine is increased, all coordination is lost. Under such circumstances a minimal sensory impulse spreads diffusely up and down the cord instead of following a simple reflex arc and eliciting a discrete motor response. As a result of this spread, numerous voluntary muscles contract. The initiating sensory stimulus can be of any nature—auditory, visual, tactile, etc.

The simultaneous contraction of many muscles under the influence of strychnine leads to what is known as a *spinal convulsion.* In this type of convulsion reciprocal inhibition of antagonistic muscles is lost, and the final effect is determined by the stronger muscle groups. The spinal convulsion is also known as *symmetrical,* inasmuch as the contractions are bilateral and simultaneous, and *incoordinate,* for all coordination is lost in a tetanic type of response. The descriptive term *tonic* convulsion has likewise been applied.

Localization of Action. The localization of strychnine action to the spinal cord is readily demonstrable. As early as 1819, Magendie showed that strychnine spasms must be of central origin. He ligated the hind leg of a frog except for the sciatic nerve and then observed that the injection of strychnine into the ligated limb had no effect whereas the systemic administration of the drug produced a characteristic response even in the ligated leg. Other classical experiments have shown that the successive ablation of the cortex, subcortical motor centers and medulla do not prevent strychnine convulsions. The exact localization of action in the spinal cord proved to be more difficult. The problem to be solved was whether both the sensory and motor elements of the reflex arc must be poisoned by the drug in order that typical effects may be obtained. The most careful work in this field has been done by Dusser de Barenne who reviewed the entire subject in 1933. Dusser de Barenne applied strychnine solution directly to the spinal cord of mammals and observed the following reactions. When the drug was applied locally to the dorsal sensory area of a spinal cord segment, a well-defined response was elicited. It consisted of paroxysmal spontaneous paresthetic disturbances, hyperesthesia and hyperalgesia of the skin area receiving its innervation from the poisoned cord segment, a hypersensitivity of the corresponding deeper structures and a hyper-reflexia evidenced by irregular twitch-like contractions. Characteristic tetanus was not observed. On the other hand, if strychnine was applied to the ventral motor area of the spinal cord the response was limited to short twitch-like contractions of muscle without demonstrable tetanus. After applying strychnine both to the sensory and motor portions of the cord a characteristic tetanus resulted.

In Dusser de Barenne's most striking experiments, strychnine was first placed on the dorsal surface of the cord in the region of the arm segments. The sensory disturbances described were observed in the arm. The drug was then applied to the ventral surface of the cord in the region of the hind limb segments. Sensory stimulation of the hind limb led to no abnormal response, for the stimulus did not pass through a poisoned sensory area of the cord. On the other hand, sensory stimulation of the fore limb resulted in a tetanic contraction of the hind limb. Dusser de Barenne concluded, therefore, that strychnine must act on the cells of both the sensory and motor regions of the cord before it elicits characteristic responses.

Cortex. The action of strychnine is not limited to the spinal cord. The sensory cortex is also sensitized by the drug and as a result the senses of taste, touch and smell are made more acute. Visual acuity also improves after the administration of strychnine but some investigators believe that this may be due to a local effect on retinal cells rather than to a central action. In support of this view is the observation that the local administration of strychnine to one eye increases the visual acuity of that eye.

Medulla. Strychnine has a stimulating action on the medulla which would be useful in therapeutics were it not for the fact that large doses are necessary to produce it. Reflex hyperexcitability of the spinal cord always accompanies medullary stimulation by strychnine except in instances when the cord is depressed. The mechanism of action on the medulla is similar to that described for the spinal cord. It is probable that strychnine has no direct stimulating effect but rather sensitizes the medulla so that it responds in an exaggerated manner to the impulses which it is constantly receiving, and also to subminimal stimuli (Travell and Gold, 1935). When the term "strychnine stimulation" is used, it refers to this mode of action. The vasomotor and respiratory centers particularly manifest sensitization by strychnine. The drug in high dosage raises the blood pressure by central vasomotor stimulation. The elevation in blood pressure can be strikingly demonstrated in an animal curarized to prevent convulsions. Strychnine affects the respiratory center in an analogous manner. It is possible to antagonize with strychnine the medullary depression produced by toxic doses of barbiturates and other hypnotics. The spinal cord is usually sufficiently depressed under these circumstances to prevent strychnine convulsions.

In usual therapeutic doses, strychnine has no demonstrable effect on either the vasomotor or respiratory centers. This fact is often overlooked, and much of strychnine therapy is based upon the false premise that a small dose of the drug produces, in lesser degree, the same actions as a large dose.

Strychnine stimulation of the central nervous system is followed by depression. In fact death from strychnine poisoning is the result of respiratory failure resulting from medullary paralysis.

Peripheral Nerves. In very high dosage, strychnine has a depressant action on the transmission of impulses to skeletal muscle. This action can only be demonstrated in isolated nerve muscle preparations, for in the intact animal death supervenes before a sufficiently high concentration of strychnine can be reached. The site of action may be on the receptive mechanism of muscle rather than on nerve fibers. If this is true, strychnine may act in a manner similar to that of curare. In fact, some forms of curare have strychnine-like properties and are obtained from certain species of Strychnos plants.

Mechanism of Action. The mechanism of strychnine action on the central nervous system has been the subject of considerable investigation. Most theories are merely descriptive rather than explanatory. For example, the convulsive action has been ascribed to a lowering of chronaxie, a loss of reciprocal inhibition of antagonistic muscles, or a lowered resistance to the passage of impulses through the spinal cord.

The most illuminating contribution to the manner of strychnine action has been made by Heinbecker and Bartley (1939) who studied the effects of the alkaloid on the basic properties of nerve cell bodies and axons. Strychnine apparently acts similarly on all portions of the central and peripheral nervous system, but its greatest effect is on the cerebrospinal axis where the chief locus of action is directly on the nerve cell body. The drug lowers the threshold of excitability and diminishes accommodation (accommodation being the increase in threshold of excitability of a nerve due to a prolonged state of excitation). Also strychnine prolongs the period of latent addition, that is, the period after stimulation during which increased excitability persists. In other words, the alkaloid renders nervous tissue more excitable by three mechanisms—by lowering the threshold of excitability, by preventing the loss of excitability from continuous stimulation, and by prolonging the period of hyperexcitability which normally follows nerve stimulation but is usually of short duration. The ganglion cells of the central nervous system which are most markedly affected by strychnine are those possessing autochthonous rhythmicity and those which on excitation produce repetitive responses in their axons. Strychnine also exhibits its typical effects on the peripheral nervous system where it acts on axons, synapses and visceral ganglion cells. High concentrations of strychnine produce opposite effects by increasing the threshold of excitability.

It is of interest to observe that Nachmansohn (1938) has shown that strychnine *in vitro* inhibits cholinesterase in concentrations compatible with those causing convulsions *in vivo*. If it should be shown that acetylcholine is involved in central synaptic transmission (page 334), it is possible that strychnine produces its excitatory effects by preserving acetylcholine.

Cardiovascular System. Strychnine has no important action on the cardiovascular system and there is no basis for its use as a stimulant for a failing circulation. The drug has no peripheral effect on the heart or on the blood vessels. It is possible to stimulate the isolated perfused heart with strychnine, but the concentration necessary to evoke this response is far in excess of that obtained clinically. In high doses, strychnine raises the blood pressure, but this action has no therapeutic significance inasmuch as it is of central origin and the response is always accompanied by convulsions unless the spinal cord is depressed. When a therapeutic dose of strychnine is administered to man, no consistent blood pressure response can be observed.

Gastro-intestinal Tract. Strychnine has an undeserved reputation as a drug capable of stimulating the smooth muscle of the gastro-intestinal tract. The action of strychnine on the intestinal musculature was first brought into prominence by the work of Langley and Magnus (1905). These investigators studied the action of the drug applied directly to the intestine of anesthetized animals or to isolated intestinal strips. They reported that strychnine was a definite stimulant to intestinal activity. It is this work which has largely been responsible for the therapeutic use of strychnine for atonic constipation and in cathartic combinations. Yonkman (1929), working with unanesthetized dogs with intestinal fistulas, also came to the conclusion that strychnine increased all phases of muscular activity of the intestine without causing an increase in reflex excitability of the nervous system. Gruber, Bryan and Richardson (1932) have taken exception to the aforementioned results. From their animal experiments they concluded that strychnine is of questionable value as an intestinal stimulant and that it is impossible to interpret accurately tracings obtained from intestinal movements due to associated skeletal muscle contractions caused by the drug. Furthermore, experiments on patients with intestinal fistulas at various levels have failed to indicate any effect of strychnine medication on the motility or tone of the human bowel. For example, Yonkman and Singh (1934) reported that strychnine in doses of two to three mgm had little or no effect in promoting the activity of the human colon as tested in patients with colostomies (Figure 23). Thus, the action of strychnine on the gastro-intestinal tract is not such as to recommend the drug as a therapeutic agent.

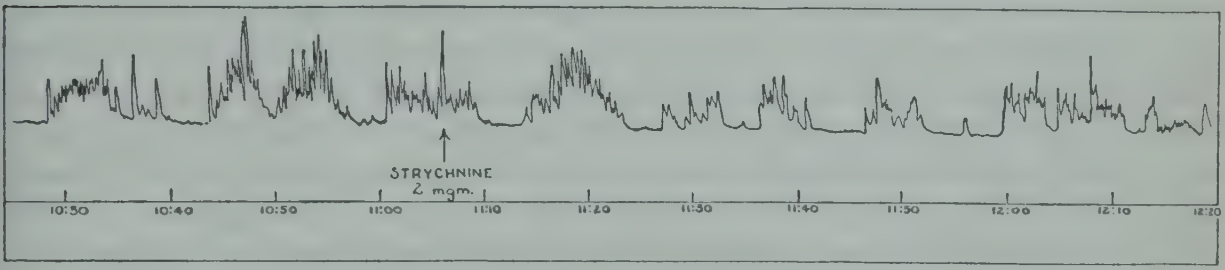


FIGURE 23. *The inefficacy of strychnine as a stimulant of the intestinal musculature in man.* The kymographic tracing was obtained by means of a balloon inserted through a colostomy into the large intestine of a patient. The balloon was connected through a water manometer to a modified Brodie air bellows. The intramuscular injection of two mgm of strychnine sulfate had no demonstrable effect on the tone or motility of the colon. (After Yonkman and Singh, 1934. Courtesy of *The Journal of the American Medical Association.*)

Strychnine is an intensely bitter substance, its taste being detectable in aqueous dilutions of 1:100,000 to 1:400,000. The drug is therefore used as a stomachic and bitter. Bitters supposedly stimulate the taste buds, increase the appetite, and reflexly stimulate gastric secretion.

Skeletal Muscle. Therapeutic doses of strychnine have no direct action on skeletal muscle. The increased tone and activity of voluntary muscle which is observed to follow strychnine administration is exclusively the result of the action of toxic amounts of the drug on the central nervous system.

Absorption, Fate and Excretion. Strychnine is readily absorbed from the gastro-intestinal tract and parenteral sites of injection. It is carried in the blood by both the serum and cells and rapidly leaves the circulation for the tissues. The central nervous system does not contain a higher concentration of the drug than do other organs. Strychnine is readily destroyed in the body, mainly by the liver. Approximately 20 per cent of the alkaloid escapes into the urine. Urinary excretion of the drug starts within a few minutes after administration and is practically complete within 10 hours, although traces may be found for several days.

The rate of destruction of strychnine is such that approximately two lethal doses can be given over a period of 24 hours without noticeable toxic symptoms or cumulative effects. The toxic dose after subcutaneous administration is only one-half to one-third that of the oral dose.

Tolerance. Tolerance to strychnine does not develop. In fact it has been claimed that with continued administration of the drug the central nervous system becomes sensitized to its action.

Toxicology. Poisoning by strychnine is not rare. The drug is not employed as a suicidal agent as often as formerly, mainly because the central nervous system depressants are at present in favor. The incidence of accidental strychnine poisoning in children, however, is surprisingly high (Aikman, 1930; Ross and Brown, 1935). The sugar-coated A.S. and B. cathartic pills (N.F.) have been the cause of a number of these accidental strychnine poisonings.

The symptoms of strychnine poisoning are mainly those of central nervous system stimulation. The first effect is noticed in the muscles of the neck and face where a definite stiffness is felt. This is followed by heightened reflex activity. The slightest stimulus causes a violent response which in the early stages of poisoning is coordinate in character. As the action of the drug proceeds, spontaneous muscle twitchings occur. A mild sensory stimulus may now precipitate a typical spinal convulsion. The movements at first are intermittent, but after a few seconds spinal tetanus appears, involving all muscles in a symmetrical fashion. Inasmuch as the stronger muscles always predominate, a typical posture ensues. In man, the body is arched in hyperextension (opisthotonos) so that only the crown of the head and the heels of the patient may be touching the ground. The legs are adducted and extended and the feet turned inward. The arms may be strongly flexed over the chest or rigidly extended. The fists are clenched. The jaw is rigidly clamped and the strong contraction of the facial muscles produces a hideous grin which has been called *risus sardonicus*. The diaphragm is involved in the general muscular contraction and this, coupled with the spasm of the thoracic and abdominal muscles, arrests respiration. Exophthalmos, mydriasis, and cyanosis also occur.

To appreciate the subjective feelings of an individual during a strychnine convulsion, one need only recall that strychnine stimulates the sensory cortex and that the patient is not only conscious but unusually appreciative of all sensations accompanying the violent muscular activity. The muscle contractions are quite painful and the patient remains acutely apprehensive and fearful of impending death throughout the ordeal.

The convulsions last approximately a minute or more after which the muscles relax and respiration is resumed. A period of depression follows the convulsion. If the convulsion has been an unusually long one, the patient may be rendered unconscious due to the apnea and anoxemia. During the period of depression, reflex irritability is low. A second convulsive seizure usually follows the first by not more than 10 or 15 minutes. Death commonly follows the second to fifth seizure, but it may ensue from the initial convulsion. Death results from medullary paralysis. This is due not only to excessive stimulation but also to anoxia resulting from the apnea.

Treatment of Strychnine Poisoning. The object of therapy in strychnine poisoning is to prevent convulsions and protect the medulla from anoxia and excessive stimulation. By the use of central nervous system depressants it is possible to antagonize the action of strychnine and abolish completely all abnormal motor activity. Formerly, morphine was commonly employed for this purpose. This was an unfortunate choice because morphine is depressant to the medulla and also heightens reflex excitability of the cord. Rational therapy requires the use of the barbiturates in strychnine poisoning. There is such a marked degree of antagonism between the actions of strychnine and the barbiturates that under laboratory conditions it is possible to protect animals from thirty-five minimal lethal doses of strychnine. Barbiturates depress hyperexcitability of the spinal cord and their depressant action on the higher centers also blocks many stimuli entering the cord from above. The barbiturates thus protect the medulla mainly by preventing strychnine convulsions. In addition, they counteract excessive excitability of the medulla itself.

It is obvious that when two antagonistic drugs are so balanced with respect to intensity of action on a particular vital center, the removal of one of them would lead to an unchecked and probably toxic action of the other. Therefore, in treating strychnine poisoning with a barbiturate, it is essential to select a preparation that has a duration of action no longer than that of the poison itself. Inasmuch as strychnine is destroyed with moderate rapidity, the preparation of choice is a short-acting barbiturate. If its action wears off too soon, more of the drug can be given. In this way, the reflex excitability of the central nervous system can be maintained within fairly normal limits until the strychnine has been completely detoxified and excreted.

The first step in the therapy of strychnine poisoning is the intravenous injection of a soluble short-acting barbiturate. Evacuation of the stomach must be postponed because the passage of a stomach tube or administration of an emetic may precipitate a convulsion. The sodium salts of both pentobarbital and amytal are very effective. The route of injection is usually intravenous for rapidity of action is essential inasmuch as each succeeding convulsion greatly reduces the patient's chance for recovery. The barbiturates are injected slowly, 10 per cent solutions usually being employed. The dose of sodium amytal is from 0.4 to 1.0 gram, and of pentobarbital-sodium, 0.3 to 0.7 gram. However, one cannot be dogmatic about dosage. The drug should be injected until the desired condition is obtained, namely, a degree of depression sufficient to antagonize convulsions and keep the patient asleep, and yet not so deep as to depress respiration or blood pressure.

Gastric lavage may now be performed if there is a possibility that some of the poison still remains in the stomach. Potassium permanganate is an effective chemical antidote and may be used for gastric lavage in a 1:1000 concentration. Tincture of iodine diluted with water (1:250) or tannic acid solution (2.0 per cent, or in the form of strong tea) may also be employed.

The patient should be kept under careful observation for many hours and protected from all possible stimuli. Wakefulness, muscle twitchings and increased reflex excitability are the signs that warn of the necessity for additional barbiturate. On the other hand, if excessive amounts of barbiturate have been given, it may be necessary to administer a respiratory stimulant or artificial respiration.

Central depressants other than the barbiturates may be employed in strychnine poisoning if barbiturates are not available. The inhalation anesthetics may be used temporarily to control convulsions until a barbiturate can be obtained. Chloroform is preferred because it is more potent and less irritating than ether. Chloral hydrate or paraldehyde may also be given. Avertin has been successfully employed.

The barbiturates have the distinct advantage of rapidity of onset of action and ease of administration.

Preparations. The official commonly employed preparations of strychnine are as follows: *Tincture of Nux Vomica,* U.S.P., contains 1.1 to 1.2 mgm of strychnine in each cc.; B.P., 2.5 mgm in each two cc. Its dose is 0.6 to 1.0 cc. *Extract of Nux Vomica,* U.S.P., contains about 7.5 per cent strychnine. Its dose is 15 mgm. *Dry Extract of Nux Vomica,* B.P., contains five per cent strychnine. The salts of strychnine are *Strychnine Sulfate,* U.S.P., *Strychnine Nitrate,* U.S.P., and *Strychnine Hydrochloride,* B.P. All possess the characteristic physical properties of alkaloids. The dose of either is one to two mgm. Strychnine in combination with iron and quinine (*Elixir of Iron, Quinine and Strychnine,* N.F.) is an irrational and complex mixture commonly employed as a tonic. Its dose is four cc.

Therapeutic Uses. Strychnine has an undeserved reputation as a useful therapeutic agent. To the drug have been ascribed properties which it does not possess or exhibits only when administered in toxic doses. Pharmacological studies have shown that many of the therapeutic applications of strychnine have little or no rationale; yet, like alcohol, the drug has a background of long usage and it continues to enjoy unwarranted popularity.

Strychnine is extensively employed as a *tonic.* This "tonic" effect is supposedly comprised of three aspects of strychnine action—the bitter taste, stimulation of the gastro-intestinal tract, and an increase in tone of voluntary muscle. As a bitter, strychnine is in no way unique. The remaining two actions are not manifested by therapeutic doses. Indeed, it is questionable whether the drug affects the motility of the enteric tract at all. The practice of administering strychnine intramuscularly as a tonic can only be censured, for even if the drug were of therapeutic value absorption following oral administration is both adequate and rapid. Parenteral therapy, in addition, is inconvenient and expensive.

Strychnine is sometimes used to *increase skeletal muscle tone* in unconscious patients, as for example, immediately following general anesthesia. Strychnine, however, enhances muscle tone only in doses just short of the convulsive, for this response is dependent upon stimulation of the spinal cord. In the doses usually employed, the drug is inactive. This is fortunate because an effective amount would endanger the patient.

There is no rational basis for the employment of strychnine in lesions of the *nervous system.* Stimulation by strychnine has no beneficial influence on any infectious, toxic, traumatic, or vascular lesion of the brain, spinal cord or peripheral nerves.

The action of strychnine on the *cardiovascular* system does not warrant its use in circulatory disorders. Any effect which strychnine has on the circulation is the result of central vasomotor stimulation and this is observed only when convulsive doses of the drug are given.

Strychnine is a valuable *respiratory stimulant* when the central nervous system is depressed to a degree which allows effective doses to be given with safety.

Consequently, strychnine is useful in the treatment of poisoning by the central nervous system depressants, especially the barbiturates (page 142).

PICROTOXIN

Picrotoxin is obtained from the *Cocculus indicus,* a climbing shrub indigenous to Malabar and the East Indies. The drug is present in the berries of the plant, commonly known as fishberries, a name derived from the native practice of throwing the bruised berries upon the water as a means of catching fish. The fish, after devouring the berries, are incapacitated and rise to the surface.

Chemistry. Picrotoxin is a non-nitrogenous neutral principle having the empirical formula $C_{30}H_{34}O_{13}$. It can be broken down to *picrotoxinin,* an active substance resembling picrotoxin in its pharmacological properties, and *picrotin* which is inactive.

Pharmacological Actions. *Central Nervous System.* Picrotoxin is a powerful central nervous system stimulant. Its site of action is higher in the cerebrospinal axis than is that of strychnine. In mammals, picrotoxin stimulates the cortex although its most prominent effect is on the midbrain and medulla. With large doses, the cord is also affected.

In an unanesthetized animal or man, the actions of picrotoxin are purely toxic. No appreciable effect is seen until convulsive doses are given. Then all portions of the central nervous system seem to share in the stimulation; confusion followed by unconsciousness indicates that the drug first stimulates and then depresses the cortex. The actions of the drug are most prominent on the lower centers, especially the medulla. The vomiting, respiratory and vasomotor centers are all stimulated. Salivation and emesis commonly occur. Vasomotor stimulation results in an elevated blood pressure. At the same time, however, there may be central vagal stimulation which markedly slows the heart. Initial respiratory stimulation is quite evident.

In large doses, picrotoxin causes convulsions. In mammals picrotoxin convulsions are altered in character by ablation of the cortex and disappear after destruction of the pons. Inasmuch as they arise from the higher centers, they are quite coordinated. Such a convulsion, in contrast with the type produced by strychnine, has been termed asymmetrical, clonic, and coordinated. Reciprocal innervation is not lost, and the limbs are alternately extended and flexed. Eventually the stimulation of the central nervous system produced by picrotoxin is followed by depression. Death results from respiratory failure.

Picrotoxin Antagonism of Central Depressant Drugs. One of the most interesting actions of picrotoxin, first mentioned by Maloney, Fitch and Tatum (1931), is its ability to combat the central depression which results from the administration of high doses of barbiturates. This analeptic action is striking and one can protect experimental animals against toxic doses of the barbiturates by the use of picrotoxin. The drug is the most effective of all the central nervous system stimulants in this respect (Das, 1939). In clinical poisoning by the barbiturates, the drug reinstates adequate respiration and greatly lightens the degree of anesthesia.

The stimulating effect of picrotoxin on depressed respiration has been studied especially by Marshall and coworkers (1937). These investigators observed that picrotoxin stimulated the respiration in anesthetized animals but in normal or decerebrate animals convulsive doses had to be given before any respiratory effects were obtained. The drug was effective in combating the depressant actions of chlorbutanol, paraldehyde and avertin, but was quite useless in alcoholic depression. They concluded that the action of the drug was not directly on the medulla, but rather that it stimulated respiration indirectly by decreasing narcosis.

Koppanyi and coworkers (1936) studied the effect of picrotoxin in experimental morphine poisoning. They observed that, although picrotoxin temporarily supported the respiration and circulation in morphine-poisoned animals, the stimulating action of morphine on the cord so combined with the central stimulation of picrotoxin that the two drugs were synergistic in producing convulsions. Thus the minimal lethal dose of morphine was lowered by picrotoxin.

Absorption, Fate and Excretion. Although picrotoxin is absorbed from all channels, it is usually given intravenously. Following its intravenous administration to experimental animals, the drug rapidly leaves the circulation and after 20 minutes only traces can be detected in the blood (Duff and Dille, 1939). Its distribution in the body is unknown. Picrotoxin is probably destroyed quite readily and this accounts for the clinical practice of administering small doses frequently for a sustained effect. If very large amounts are injected, a portion can be recovered in the urine.

Toxicology. Picrotoxin is a highly toxic substance and a dose of 20 mgm may produce symptoms of severe poisoning. The fatal dose for human beings is unknown. The symptoms of picrotoxin poisoning are those described under its central actions. A barbiturate is the best antidote for poisoning by picrotoxin and the procedure outlined for the treatment of strychnine poisoning, except for the use of chemical antidotes, applies also to picrotoxin.

Preparations. Picrotoxin is not an official drug, and preparations are not readily available. It can be obtained, however, in the form of the crystalline compound.

Therapeutic Uses. The only therapeutic use for picrotoxin is in the treatment of poisoning by the central nervous system depressants, notably the barbiturates. Although the drug has but a short clinical history, favorable reports have appeared in the literature and from the available evidence it appears that picrotoxin may be an effective physiological antagonist to the barbiturates.

In the treatment of *barbiturate poisoning*, picrotoxin is administered by intravenous injection. No didactic statement regarding dosage can be made. Rather the drug is given until the return of the corneal and pupillary reflexes. Bleckwenn and Masten (1938) recommend that the drug be injected in a 1:1000 concentration in isotonic saline solution at the rate of one cc (one mgm) a minute until the desired effect on reflex activity is obtained. Repeated injections may be necessary if the patient again relapses into a deep narcosis. However, consciousness may remain in abeyance despite the return of reflexes (Rovenstine, 1938). An individual poisoned with a barbiturate is often extremely tolerant to picrotoxin and during treatment usually receives amounts of the drug which would be fatal to a normal individual. Total doses often range between 50 and 150 mgm given over a period of several hours. Kohn and coworkers (1938) report the successful treatment of a case of barbiturate poisoning with a total of 671 mgm of picrotoxin.

From laboratory evidence it is possible that picrotoxin may prove of value in the treatment of poisoning from central depressants other than the barbiturates. However, it seems to be contraindicated in the treatment of morphine poisoning as also is strychnine.

Therapy of barbiturate poisoning should not be limited to the injection of picrotoxin. Other drugs and supportive measures are also indicated (page 142). The status of the use of picrotoxin in poisoning by the barbiturates has been reviewed by the Council (1939), and by Reifenstein and coworkers (1939).

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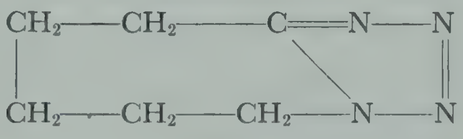
CHAPTER 16

METRAZOL, CORAMINE AND CAMPHOR

METRAZOL

Metrazol (cardiazol) is a synthetic compound which possesses to a high degree the property of stimulating the central nervous system. Chemically, it is related to camphor inasmuch as in metrazol the six carbon ketone ring of camphor has been condensed to form pentamethylenetetrazol. The structural formula is as follows:



Metrazol

Pharmacological Actions. *Central Nervous System.* Metrazol is a central nervous system stimulant. Its action is primarily on the higher centers but all parts of the cerebrospinal axis are stimulated to some degree. When given in high dosage to experimental animals, metrazol first causes marked restlessness which is followed by excitement, increased motor activity and typical epileptiform convulsions. The convulsions can still be elicited after removal of the cerebrum above the thalamus. With successive ablation of lower segments of the brain stem, the convulsive dose of metrazol becomes greater.

The medulla also shares in the stimulation. Respiration is markedly increased by large doses of metrazol. The vasomotor and vagal centers of the medulla are likewise stimulated.

The reflex activity of the cord is increased. In fact, when large amounts of metrazol are administered, the epileptiform convulsions may terminate in typical tonic convulsions. The action of metrazol on the spinal cord is especially evident if the reflex activity of the cord has been lowered by central nervous system depressants. In such a case, a relatively small dose of metrazol will restore spinal reflexes toward normal. There appears to be a definite limit in the ability of metrazol to restore to normal the functions of the depressed spinal cord. Koll (1937) noted that once the maximal action of the drug was obtained, it could not be enhanced by the injection of additional amounts. However, if strychnine were now injected, a further increase in reflex activity was obtained. Likewise, Koll observed that metrazol was capable of increasing reflex excitability after strychnine had been allowed to exert its maximal effect.

The analeptic action of metrazol on the higher centers of the central nervous system is evident from its ability to counteract the depression produced by hypnotic drugs. This is prominent when directed against the depression caused by barbiturates, avertin, paraldehyde and chloral hydrate. So marked is the antagonism of metrazol to avertin that experiments have been described in which animals with complete motor paralysis have been restored to normal immediately after the administration of metrazol. Not only is motor activity restored, but failing respiration and circulation are stimulated through the medullary action of the drug. The effect of metrazol on the medulla is much more prominent when this region is depressed than when it is functioning normally. The action is probably a direct one for typical effects on blood pressure and respiration can be obtained after the carotid sinus and carotid body have been completely denervated. As a result of this analeptic action, metrazol can protect against toxic doses of central depressants. Likewise, individuals depressed by hypnotics (*e.g.,* amytal) are more resistant to the actions of metrazol (Cohen, 1939).

Circulation. Metrazol has been widely heralded as a circulatory stimulant but its peripheral action on the heart and blood vessels is negligible. It has no definite cardiac effect when perfused through the isolated mammalian heart. Neither does it improve the coronary circulation to a significant degree. It has no constrictor action on the musculature of blood vessels. Indeed, the drug may produce splanchnic vasodilatation (Haury and Gruber, 1939). The cerebral vessels are also dilated by metrazol (Forbes and Nason, 1940). Clinically, the circulatory effects of metrazol are due entirely to its action on the medulla. When the circulation has been depressed by a hypnotic agent, a marked rise in blood pressure can be noticed after the injection of metrazol as a result of central vasomotor stimulation. However, when the drug is given to a normal individual or to a patient whose circulation is depressed by other than central mechanisms, no such response is obtained. Indeed, the pressure may fall due to the bradycardia which results from central vagal stimulation.

Messinger and Moros (1940) studied the cardiovascular effects on human beings of convulsive doses of metrazol as employed in the treatment of schizophrenia. No pronounced or prolonged alterations in blood pressure could be attributed to the action of the drug. In some instances transitory cardiac irregularities, most often auricular extrasystoles and sinus arrhythmia, were observed. Rarely were ventricular extrasystoles noted. Messinger and Moros conducted their investigations primarily to establish whether metrazol was contraindicated in the treatment of schizophrenic patients with organic heart disease. So innocuous were the effects of large doses of the drug on the cardiovascular system that they concluded that metrazol was of little value as a cardiac stimulant.

Toxicology. Metrazol is a relatively non-toxic drug insofar as the amount necessary to produce serious poisoning is concerned. Two hundred milligrams may be given intravenously in human beings without danger. Death has been reported from the ingestion of 10 grams. The symptoms are typical of those produced by the central nervous system stimulants having actions on the higher motor centers and the spinal cord, and consist of clonic and tonic convulsions. The convulsions are spontaneous in origin and not induced by external stimuli. They last for several minutes and are followed by profound depression. Death results from anoxemia, medullary depression and respiratory paralysis.

The repeated injection of convulsive but non-fatal doses of metrazol in experimental animals (three times weekly for a total of 14 to 18 injections) causes pathological changes in the brain (Whitehead and coworkers, 1940). The lesions consist of diffuse degenerative changes of moderate degree in nerve cells and complete necrosis of the nervous parenchyma in circumscribed areas of the cortex.

The lesions are attributable to the periods of cerebral anoxia which attend metrazol convulsions.

Metrazol Convulsions in Man. Metrazol has been extensively employed in the treatment of schizophrenia, and this has offered the opportunity to study metrazol convulsions under controlled conditions. The observations of Finkelman and coworkers (1938) on metrazol convulsions in man are quoted verbatim because, in a broad sense, they apply to the actions of any drug capable of stimulating the brain and cord and producing both clonic and tonic convulsions.

"From two to five seconds after the intravenous administration of metrazol the patient coughs, and five seconds later marked pallor of the face occurs. From three to ten seconds after the injection an intense blepharospasm occurs and the facial expression is a mixture of bewilderment and fear. Five seconds later myoclonic convulsive movements begin in the face, shoulders and arms, sometimes only on one side. A well marked rhythmic clonic phase develops. . . . After about fifteen seconds a tonic phase ensues. The head is retracted and the back arched. The eyeballs may move upward or to either side or remain in the original plane. The arms and legs are tetanically contracted in extension. The wrists and fingers are flexed, the position of the thumb frequently being between the index and the middle finger. Sometimes before the opisthotonos there is a flexion of the thighs, legs and feet, with the large toes in the Babinski position. This is followed by an extension of the lower extremities. Frequently there is an adductor spasm, with the legs in a scissor-like position. These positions of the body may change during the tonic phase; the knees may be flexed on one side and extended on the other. There may be a rotation of the pelvis to one or the other side, with flexion of the thighs and legs, followed by an extension. Similarly, the upper extremities may assume various postures.

"The tonic phase lasts from five to thirty seconds and is followed by another clonic phase. The first clonic movements break through in the fingers and spread to involve the entire body. Such rhythmic clonic movements are seen while the extremities are still held in tonic extension. The clonic movements are at first rapid, gradually become less frequent with increasing amplitude and cease after about twenty-five seconds. During this stage ejaculation may occur. Urination is observed after relaxation. During the tonic phase and the succeeding clonic one, there is a period of apnea, with marked cyanosis. After a few seconds the patient resumes breathing. A pilomotor reaction is present during the tonic phase and gradually disappears during the apneic period. Sometimes the lower extremities and not infrequently the upper extremities are rigidly extended after the second clonic phase. After the convulsion the patient frequently is drowsy and may fall asleep. About one minute after the last clonic phase a period of restlessness may occur. The patient may thrash his arms about, or there may be a definite pattern of movements, such as rolling of the body to the side. About five minutes after the injection the patient's attention may be attracted by verbal stimuli. As a rule each individual has his own constant motor pattern. The patient may show some motor restlessness immediately before the first clonic phase, such as flapping his arms as in 'wing beating,' brushing his face or alternately raising or lowering legs.

"In the majority of cases there is a short period of areflexia soon after the convulsion, which is followed in a few seconds by increased deep reflexes, sustained ankle clonus and the Babinski sign. Usually there is a short period of confusion after the seizure. In some patients the confusion may last several hours. The patient has total amnesia for the phenomena, recalling only the injection and a feeling of anxiety. One patient counted to thirty after the injection but after the reaction stated that he recalled counting only to twelve.

"The pupils are dilated during the convulsion and do not react to light. In some cases there is profuse perspiration after the convulsion. The blood pressure rises from 20 to 60 mm. of mercury during the seizure and drops to its normal level in from ten to thirty minutes."

Absorption, Fate and Excretion. Metrazol is rapidly absorbed from all sites of administration. Indeed, so rapid is its absorption that there is slight difference in the latent period before its action appears after peroral, subcutaneous and intravenous administration. Metrazol is also very rapidly detoxified, probably by the liver, and in experimental animals 50 per cent of a convulsive dose can be given at two hour intervals without eliciting toxic symptoms. The clinical action of metrazol is thus evanescent. The metrazol molecule is stable, a fact suggesting that the drug is detoxified by conjugation rather than by destruction. Metrazol cannot be demonstrated in the urine in an unchanged or active form.

Preparations. *Metrazol,* N.N.R., is a white crystalline powder soluble in water. It is available in 100 mgm tablets and as a 10 per cent solution, either in bulk for oral administration or in sterile ampules containing one cc (100 mgm) or three cc (300 mgm).

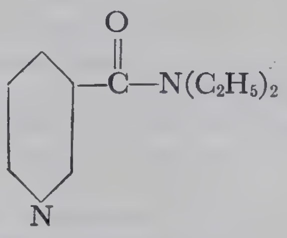
Therapeutic Uses. Metrazol is recommended as a central nervous system and cardiovascular stimulant. It is of value in the *treatment of poisoning by central depressants* but is probably less effective than strychnine, picrotoxin, caffeine or ephedrine. The drug, however, is rapidly detoxified and therefore its action can be well controlled. Metrazol has also been employed as an *analeptic* to lessen the degree of anesthesia. Pharmacological evidence does not encourage the use of metrazol as a cardiovascular stimulant. It is of doubtful value in circulatory collapse other than that due to central vasomotor depression, and is not indicated in shock. The dose usually employed for parenteral administration is 0.1 to 0.3 gram (one to three cc).

Metrazol has been used in the treatment of *schizophrenia.* The drug is given intravenously in amounts sufficient to cause convulsions (usually from three to seven cc). It is claimed that remission of symptoms in a fair percentage of cases follows a course of metrazol convulsions. It is impossible to state the exact mechanism of action (*see* insulin convulsions, page 1225) or properly to evaluate the true worth of the drug in mental disorders. The procedure involves definite risks to life, and should be undertaken only by psychiatrists especially trained in this field. The acute anterior flexion of the body induced by the metrazol convulsion may cause a high incidence (22 cases in 51 patients) of compression fractures of the thoracic vertebrae (Polatin and coworkers, 1939). Similar observations have been recorded by Bennett and Fitzpatrick (1939) and Hamsa and Bennett (1939).

CORAMINE

(NIKETHAMIDE)

Coramine is a pyridine derivative with the following structural formula:



Coramine

The compound is a synthetic, water-soluble, light viscous oil which was introduced into therapeutics as a respiratory and cardiac stimulant.

Pharmacological Actions. *Central Nervous System:* Coramine is a respiratory stimulant and apparently exerts this effect in doses which have little action on other portions of the cerebrospinal axis. Respiration is stimulated reflexly by the effect of coramine on the chemoreceptors of the carotid body. In toxic amounts, coramine causes convulsions from excitation of higher motor centers. Following toxic doses, death results from respiratory paralysis. Coramine acts more powerfully on a depressed than on a normal respiratory center. It is claimed that the drug is of particular value in overcoming the respiratory depression caused by morphine (Maloney and Tatum, 1932). Coramine is also said to be more effective against the depression of respiration caused by volatile anesthetics than that produced by large doses of barbiturates.

In addition to its action on the respiration, coramine acts as an analeptic. It counteracts the anesthetic action of a variety of the central nervous system depressants, and is particularly effective in overcoming the depressant action of avertin. There is some laboratory evidence that the duration of action of the barbiturates is not shortened by coramine, but clinical data seem to indicate that the drug arouses patients from barbiturate depression. However, coramine is less effective in this respect than picrotoxin or metrazol (Burstein and Rovenstine, 1937).

Circulation. The effects of coramine on the circulation are not striking. The drug supposedly stimulates the heart muscle directly, increases coronary blood flow, and causes peripheral vasoconstriction by central vasomotor stimulation. It is also claimed to have a direct effect on the capillary walls. However, there are many investigators who have failed to observe these cardiovascular actions. The drug is probably only of benefit in treating circulatory depression of central origin.

Absorption and Route of Administration. Coramine is absorbed from all sites of administration. However, it is most effective after intravenous injection. The drug has a wide margin of safety, and in laboratory animals the toxic dose is ten times the minimal effective dose.

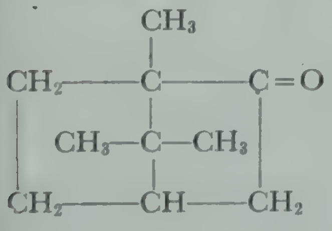
Preparation and Dosage. Coramine is neither an official preparation nor is it included in N.N.R. However, the Council has assigned to the compound the non-proprietary name "nikethamide." It is available in 25 per cent aqueous solution marketed in bulk for oral use and in sterile ampules for parenteral administration. The dose by any route is one to three cc.

Therapeutic Uses. The main therapeutic use of coramine is as a *respiratory stimulant* in the event of excessive depression following the use of central depressants. It does not compare in efficiency with strychnine, metrazol, picrotoxin or caffeine. Coramine, despite its name, is of little value as a cardiovascular stimulant and should not be the drug of choice in combating combined circulatory and respiratory depression. It is of interest to note that coramine, as well as other derivatives of nicotinic acid, has proved effective in the therapy of *pellagra* (page 1255).

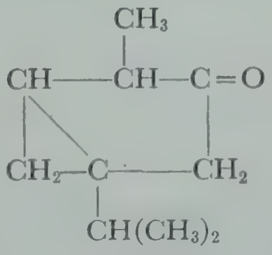
CAMPHOR

History. Camphor has been used for centuries in Chinese medicine for a variety of purposes. It was probably the odor of the compound which led to its use as a medicinal and for the same reason it has today some reputation among the laity as a valuable agent for protection against infection. Some children are still required by their parents to wear camphor bags suspended around their necks to ward off colds and other ailments.

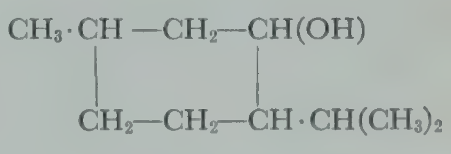
Chemistry. Camphor belongs to a group of substances known as the stearoptenes. These are crystalline compounds which are deposited from volatile oils upon standing, especially when exposed to cold. Natural camphor is obtained from the wood and bark of a tree, *Cinnamomum camphora*, growing especially in Japan and Formosa. Camphor is also obtained synthetically. Related to camphor are menthol, obtained from oil of peppermint, and thujone, an isomer of camphor which occurs in absinthe. Thujone is not used therapeutically but it has been claimed that it may cause the epileptiform convulsions occurring in chronic absinthe drinkers. The structural formulas of these three substances are as follows:



Camphor



Thujone



Menthol

Pharmacological Actions. *Local.* Locally, camphor is weakly antiseptic. It is also a rubefacient when rubbed on the skin. When not vigorously applied, however, it may produce a feeling of coolness. This is especially true of menthol. The sensation is quite noticeable in the respiratory tract when low concentrations of menthol are inhaled, as in the smoking of mentholated tobaccos. The mechanism of this action is imperfectly understood but it is thought to be due to selective stimulation of nerve endings sensitive to cold. Camphor also has a mild local anesthetic action and its application to the skin may be followed by numbness.

Camphor has a local action on the gastro-intestinal tract. It has a hot, bitter taste and when taken in small amounts produces a feeling of warmth and comfort in the stomach. In large doses it is irritating and causes nausea and vomiting.

Central Nervous System. Camphor stimulates the central nervous system. In man and mammals this action is more marked on the higher centers, although all portions of the cerebrospinal axis share it to some degree. In high doses the drug produces epileptiform convulsions which are largely cortical in origin.

The effects of non-convulsive doses of camphor on the respiration are negligible. In cases of severe depression, some stimulation of respiration may result. The greater part of this effect is probably a reflex stimulation from the pain caused by the irritating subcutaneous injection of camphor.

Circulation. The effects of camphor on the heart are inconstant, unpredictable and inconsequential. The literature on the cardiovascular actions of camphor, however, reveals considerable disagreement. The blood pressure may fall due to peripheral vasodilatation or it may rise slightly as a result of central vasomotor stimulation. During convulsions, the blood pressure rises; in the period of postconvulsive depression, it is low.

Absorption, Fate and Excretion. Camphor is readily absorbed from all sites of administration. It is oxidized to camphorol and excreted in the urine conjugated with glycuronic acid.

Camphor Poisoning. The ingestion of camphor moth balls by children is a common cause of camphor poisoning. The symptoms of poisoning are headache, a feeling of warmth, confusion, excitement, restlessness, delirium and hallucinations. Stimulation ultimately results in unconsciousness and epileptiform convulsions which are followed by periods of extreme depression. On rare occasions, excitement phenomena are not seen and depression is the primary symptom. Death results from respiratory failure. Treatment is the same as for other central stimulants and is largely symptomatic (*see* strychnine poisoning, page 260).

Preparations, Doses and Routes of Administration. *Camphor,* U.S.P., B.P., is a transparent, aromatic, crystalline substance. It is relatively insoluble in water. Orally, the drug is administered in crystalline form in gelatin capsules. It is dissolved in oil, usually as a 20 per cent solution, for hypodermic administration (*Ampuls of Camphor,* N.F.). The dose by either route is 0.2 gram. Other official camphor preparations are *Camphor Water,* U.S.P., B.P. (a saturated aqueous solution containing approximately one gram in 1000 cc), used as a vehicle; *Camphor Liniment,* U.S.P., B.P. (20 per cent in oil) and *Spirit of Camphor,* U.S.P., B.P. (10 per cent in alcohol).

Therapeutic Uses. On the skin, camphor is used as a *liniment,* analgesic and antipruritic. It is taken by mouth as a *carminative.* Despite the lack of evidence of its efficacy, camphor is widely used as a *circulatory and respiratory stimulant.* It is usually injected intramuscularly as a 20 per cent solution in oil. Its local irritant action may result in some reflex stimulation of the central nervous system. It is doubtful whether the drug has any appreciable systemic action in therapeutic doses. Camphor has a slight *expectorant* action and is a component of paregoric.

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CHAPTER 17

THE XANTHINES

CAFFEINE, THEOPHYLLINE AND THEOBROMINE

Source and History. Caffeine, theophylline and theobromine are drugs which are similar in chemical constitution and pharmacological action. They are found in a large number of plants widely distributed throughout the world. It is of interest to note that wherever these plants are indigenous, natives have used their aqueous extracts as beverages. The consumption of some of these beverages such as coffee, tea and cocoa is practiced all over the civilized world. *Coffee,* obtained from the seeds of *Coffea arabica,* contains caffeine. *Tea,* the leaves of *Thea sinensis,* contains caffeine and theophylline. *Cocoa,* obtained from the seeds of *Theobroma cacao,* contains theobromine.

In addition, a number of caffeine beverages, less universal in appeal, are consumed in widely scattered areas. *Maté* is the national drink in many South American countries. It contains caffeine. In the vast territory of the Sudan, natives chew the Kola nut and swallow the extractives. The Kola nut is a valued possession and is used as a basis for commercial exchange. This nut contains two per cent caffeine. Many species of the *Paullinia* plant grow in the Amazon basin, but only one of these, the *Paullinia sorbilis,* is used by the natives as a beverage. This species is unique in that it contains a large amount of caffeine. Many of the so-called "soft drinks" popular in the United States maintain their appeal not only because of their flavor but also because of their caffeine content.

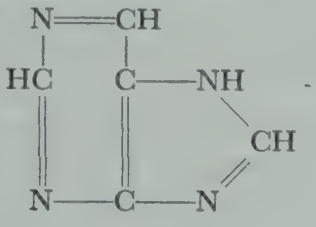
The earliest use of the xanthine beverages is lost in the obscurity of the past. However, legends telling of their discovery reveal the reason for their favor. For example, legend credits the discovery of coffee to a prior of an Arabian convent. Shepherds reported to this prior that goats which had eaten the berries of the coffee plant did not rest but gamboled and frisked about all through the night. The prior, mindful of the long nights of prayer which he had to endure, instructed the shepherds to pick the berries so that he might make a beverage from them. The success of his experiment is obvious from the popularity of coffee today, a billion pounds being consumed yearly in the United States alone.

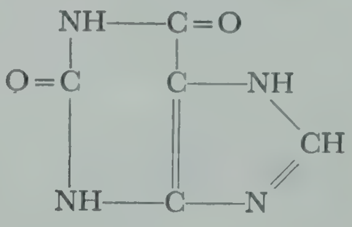
A similar story tells of the discovery of tea by Bodhidharma who lived in the sixth century A.D. Bodhidharma, the son of a king of India and an apostle of Buddhism, traveled to China to spread his beliefs. There he lived under the open sky, mortified his flesh, tamed his passions, and subsisted on leaves. He sought sanctity by attempting to stay awake for nine years while contemplating the virtues of Buddha. After three years of this practice, he fell asleep. Upon awakening, overcome with chagrin, he cut off his eyelids so that his sin might not be repeated. A plant sprang up where his eyelids had fallen. He ate its leaves and found that he could return to his worship with renewed vigor. This plant was the tea plant.

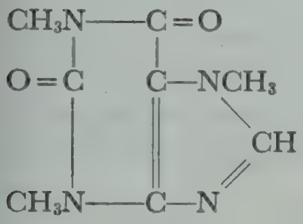
From these old tales, it can be inferred that caffeine is a stimulant, and this action is probably the basis for the popularity of the caffeine-containing beverages.

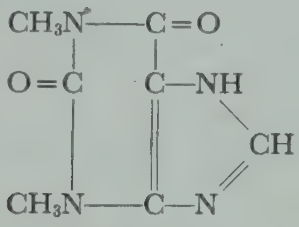
Pharmacological studies of caffeine have confirmed the stimulant property suggested by legend. The drug possesses other properties and caffeine and related compounds are valuable therapeutic agents.

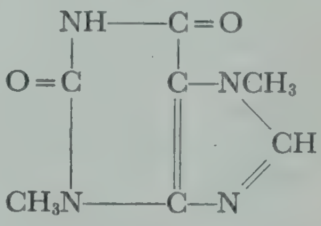
Chemistry. Caffeine, theobromine, and theophylline are methylated xanthines. They are often spoken of as "xanthine derivatives," or merely "xanthines." Xanthine itself is dioxypurine. Caffeine is 1:3:7 trimethylxanthine, theobromine 3:7 dimethylxanthine, and theophylline 1:3 dimethylxanthine. The structural formulas of purine, xanthine and the three pharmacologically important xanthine derivatives are as follows:


Purine


Xanthine


Caffeine


Theophylline


Theobromine

Pharmacological Actions

Caffeine, theobromine and theophylline are similar in their pharmacological properties but differ markedly in the intensity of their actions on various structures. Therefore, in the therapeutic application of these drugs for a specific effect, side-actions can be minimized and the desired response intensified by the selection of the proper xanthine. The properties of the xanthines which are utilized in therapeutics are the ability to stimulate the central nervous system, the action on the kidney to produce diuresis, the stimulating effect on cardiac muscle, and the relaxation of certain smooth muscle structures, notably the coronary arteries and bronchi. Table 12 depicts the relative potencies of the xanthines in producing these and other effects.

TABLE 12

RELATIVE PHARMACOLOGICAL POTENCIES OF THE XANTHINES

XANTHINE	C.N.S. STIMULATION	RESPIRATORY STIMULATION	DIURESIS	CORONARY DILATATION	CARDIAC STIMULATION	SKELETAL MUSCLE STIMULATION
Caffeine	1 *	1	3	3	3	2
Theophylline	2	2	1	1	1	3
Theobromine	3	3	2	2	2	1

* 1 = most potent

Central Nervous System. Caffeine is a powerful central nervous system stimulant, theophylline less so and theobromine comparatively benign in this respect. Caffeine is the xanthine usually employed clinically for its central action, but theophylline also has specific uses as a respiratory stimulant. Caffeine excites all portions of the central nervous system. The main sites of stimulation are the cortex, medulla and spinal cord. The cortex is first affected, next the medulla and the cord is stimulated only by very large amounts.

Cortex. Caffeine stimulates all portions of the cortex, but its main action is on psychic and sensory functions. It produces a more rapid and clearer flow of thought, and allays drowsiness and fatigue. After taking caffeine, one is capable of a more sustained intellectual effort and a more perfect association of ideas. There is also a keener appreciation of sensory stimuli. Motor activity is likewise increased. Typists, for example, have been found to work faster and with fewer errors. Reaction time to stimuli is appreciably diminished. There is evidence, however, that recently acquired motor skill in a task involving delicate muscular coordination and accurate timing may be affected adversely (Horst and coworkers, 1934).

The aforementioned effects of caffeine are obtained after the administration of therapeutic doses, that is, about 150 to 250 mgm for an adult. This represents the amount of caffeine ordinarily contained in a cup or two of coffee or tea. The average individual usually denies that he has experienced stimulation from ingesting a caffeine-containing beverage. The reason for this is that the type of stimulation derived from small amounts of caffeine is so physiological that one is usually unaware of it. It is only by careful tests that the true action of the drug can be demonstrated. All such investigations, starting with the classical ones of Kraepelin in 1892, have been consistent in demonstrating the stimulation of cortical centers by caffeine.

Excitation of the central nervous system is usually followed by depression. There has been considerable controversy, however, as to whether the mild physiological stimulation produced by small amounts of caffeine is followed by any depression. For example, in the researches of Horst and coworkers mentioned, a definite after-depression was observed as late as twenty-four hours after ingestion of caffeine. On the other hand, Cheney (1935) has reported no change in responsiveness which could be related to an after-depression.

Medulla. In addition to its action on the cortex, caffeine is a medullary stimulant. The medullary action, however, is manifested only when large doses are administered and is most clearly seen when the medulla is previously depressed, as, for example, by morphine. Caffeine acts on the respiratory, vasomotor and vagal centers in the medulla. When full therapeutic doses of caffeine are taken orally (150–250 mgm), there is little change in respiration. However, the same amount after parenteral administration definitely stimulates the respiratory center. The action of caffeine on the respiratory center is probably a direct one. The stimulation of the vasomotor and vagal centers can best be demonstrated in medullary perfusion experiments, because after systemic administration the peripheral effects of the drug on the circulation are such as to mask these central actions.

Effect of Large Doses. After the administration of large amounts of caffeine, the entire central nervous system is stimulated, including the spinal cord. Reflex excitability is increased. Excitation of the lower motor centers may lead to clonic convulsions, and if the dose is large the cord may be sufficiently affected so that tonic convulsions and death may result. However, such an extreme type of reaction has been observed only in experimental animals, for the toxic dose of caffeine for man is so large (over 10 grams) that no human fatalities have been reported.

Cardiovascular System. The xanthines have important actions on the circulatory system of which therapeutic use is made. Theophylline is the most active and caffeine the least. Even the action of caffeine on the circulation is quite powerful but the side-effects of this drug on the nervous system and metabolism preclude its clinical use for cardiovascular effects.

All parts of the circulatory system are affected in some way by the xanthines. In several instances, these varied actions are antagonistic. Therefore, the observation of a single function, as, for example, the effect of xanthines on blood pressure, is deceiving because the drugs may act on a variety of circulatory factors in such a way that the blood pressure may remain essentially unchanged. The observations of Starr and coworkers (1937) on the cardiovascular effects of xanthines in human subjects are presented in Table 13.

TABLE 13

CARDIOVASCULAR, RESPIRATORY AND METABOLIC EFFECTS OF CAFFEINE AND THEOPHYLLINE IN HUMAN SUBJECTS UNDER BASAL CONDITIONS †

	CAFFEINE WITH SODIUM BENZOATE * (0.5 gram intramuscularly)		THEOPHYLLINE ETHYLENE DIAMINE ** (0.48 gram intramuscularly)	
FUNCTION	Decrease %	Increase %	Decrease %	Increase %
Pulse rate	2.4		1.7	
Systolic pressure	4.0			6.8
Diastolic pressure	3.8			7.0
Cardiac output		14.8		25.8
Stroke volume		19.1		29.4
Left ventricular work per minute		9.3		35.4
Left ventricular work per beat		13.8		38.0
Heart volume	0.8		0.3	
Metabolic rate		6.9		7.8
Arteriovenous oxygen difference	6.1		12.4	
Respiratory rate	4.1			2.7
Respiratory volume		12.6		23.8
Peripheral circulatory resistance	14.3		18.9	

* Average results in four patients.
** Average results in seven patients.
† Data of Starr, Gamble, Margolies, Donal, Joseph and Eagle (1937).

Heart. The actions of caffeine on the heart are illustrative of the antagonistic effects which have just been mentioned. Caffeine stimulates the myocardium directly. This can readily be demonstrated in the isolated mammalian heart. The addition of xanthine to the perfusion fluid results in an increase in amplitude of excursion, rate and cardiac output. When given to an intact animal, however, in addition to stimulating the myocardium directly, the xanthines, especially caffeine, stimulate the medullary vagal nuclei. This may produce a decrease in heart rate. The ultimate effect is the net result of these two types of stimulation. Consequently, one may observe in different individuals slight bradycardia or tachycardia following the ingestion of caffeine (Horst and coworkers, 1934, 1936). After high doses of caffeine, or the injection of large amounts in experimental animals, a definite tachycardia ensues from a direct stimulation of the myocardium. Eventually this stimulation may become so great as to cause cardiac irregularities. Occasionally, arrhythmias may be encountered in persons who use caffeine beverages to excess.

The direct myocardial action of the xanthines causes an increase in cardiac output. The increase is not due to a more rapid cardiac rate for it may occur independently of tachycardia. Rather, it results either from a greater stroke volume or an accelerated venous return.

Blood Vessels. Caffeine tends to constrict blood vessels by stimulation of the medullary vasomotor center, and to dilate them by a direct effect on vascular musculature. Here again, the central and peripheral actions are antagonistic.

After therapeutic doses, the peripheral vasodilator action predominates. Oncometer studies in experimental animals show that there is a definite increase in organ volume following the administration of a xanthine. Vasodilatation, coupled with an augmented cardiac output, results in an increased blood flow.

Coronary Circulation. The coronary vessels are also relaxed by the xanthines. This has been demonstrated experimentally both in intact unanesthetized animals and in anesthetized animals when an increase in coronary circulation sometimes as great as 100 per cent follows xanthine medication (Essex and coworkers, 1940; Boyer and coworkers, 1939). The claim has been made that the xanthines also facilitate the establishment of collateral coronary circulation in dogs with experimental myocardial infarction (Fowler, Hurevitz and Smith, 1935). Wiggers and Green (1936) and Gold and coworkers (1937), however, have been unable to confirm this finding.

Experiments designed to elucidate the action of the xanthines on coronary blood flow are of considerable practical importance for the drugs are extensively employed in patients with disease of the coronary artery. The question is actively debated as to whether the vasodilator effect of the xanthines on the coronary arteries of man is sufficiently great to be of therapeutic value. Unfortunately, one cannot use a direct experimental approach to the solution of this problem. Rather a decision concerning the efficacy of the drugs must rest on clinical data obtained from studies of the relief afforded by xanthines to patients with impaired coronary circulation. The results of such investigations are discussed under the clinical uses of the xanthines.

Blood Pressure. It should be obvious from the foregoing discussion that the effect of xanthines on the systemic blood pressure is unpredictable. The actions which would favor an increase in blood pressure are central vasomotor and direct myocardial stimulation. Conversely, the factors favoring a decrease in blood pressure are central vagal stimulation and peripheral vasodilatation. The end-result on blood pressure of these opposing actions is not striking but it usually consists of a slight rise, seldom amounting to more than 10 mm of mercury. The slight elevation in pressure is mainly the result of the increase in cardiac output and occurs despite peripheral vasodilatation. The latter, in turn, masks any effect of central vasomotor stimulation. The combination of vasodilatation and enhanced cardiac output produces a more rapid blood flow and a more efficient circulation.

An unusual effect of the xanthines on blood pressure is the sharp but transitory fall which follows their rapid intravenous injection. The exact mechanism of this fall is unknown. It has been suggested that a high concentration of drug depresses the myocardium, but it is more likely that the fall in blood pressure is due to a precipitation of the xanthine alkaloids in the blood. The compounds are feebly basic and the acid salts which they form may easily be thrown out of solution when they encounter the alkaline reaction of the blood. When xanthine salts are administered intravenously, the rate of injection should be very slow.

Smooth Muscle. The xanthines act on smooth muscles other than those of blood vessels. Walters and coworkers (1937) have shown that theophylline ethylenediamine is effective in overcoming the spasm of the *biliary tract* produced in human beings by the injection of morphine, dilaudid or codeine (Figure 59). On the basis of this observation, the xanthines deserve a trial in the treatment of biliary colic. The action of the xanthines on the motor activity of the remainder of the *gastro-intestinal tract* is unimportant. Dilute solutions increase and high concentrations depress the tone and amplitude of contractions of isolated intestinal strips. In the body, however, therapeutic doses of xanthines have no significant effect on gastro-intestinal activity.

The smooth muscles of the *bronchi* are also relaxed by the xanthines especially if constricted experimentally by histamine or clinically in asthma. Greene and coworkers (1937) have obtained relief in cases of bronchial asthma following the administration of theophylline. A definite increase in vital capacity is associated with the symptomatic relief afforded by the drug. These investigators reported that asthmatics refractory to epinephrine may respond favorably to theophylline. The dyspnea of cardiac failure also reacts favorably to xanthine administration. In this condition, however, relief is due not so much to bronchial dilatation as to an improved cerebral circulation with a resulting decrease in intrathecal and venous pressures. The effect of theophylline on Cheyne-Stokes respiration associated with cardiovascular disease is shown in Figure 24.

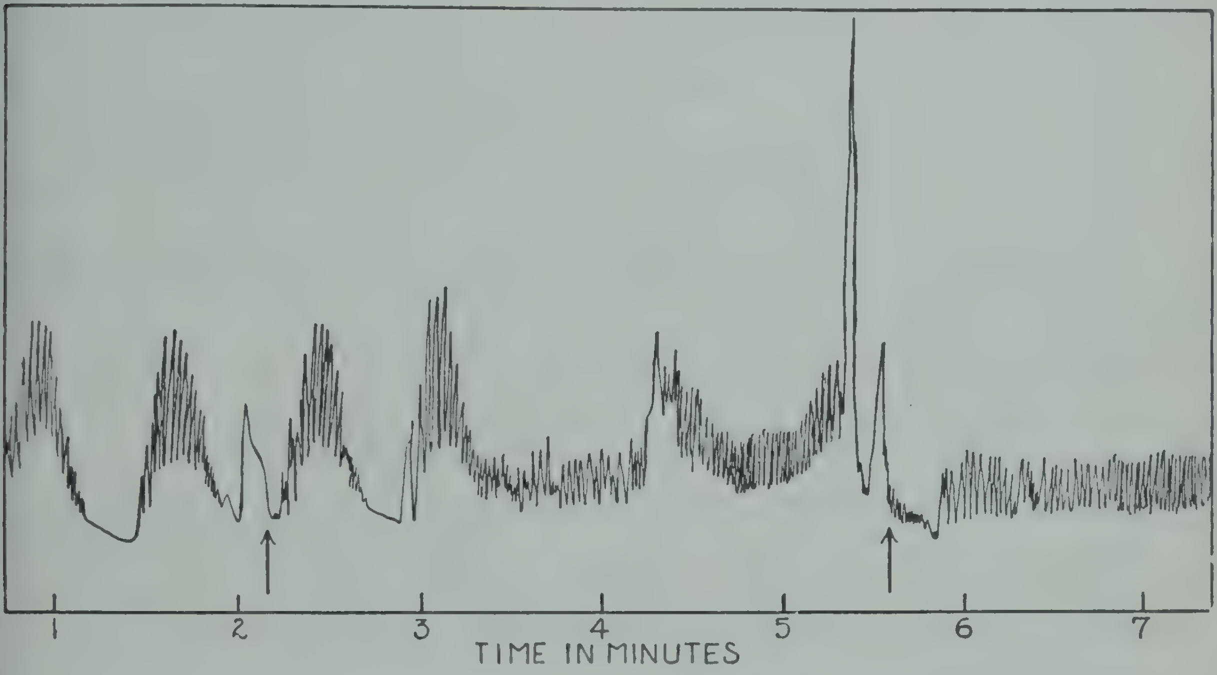


Figure 24. *The effect of theophylline on Cheyne-Stokes respiration.*

Plethysmographic tracing of respiratory movements in a patient with Cheyne-Stokes breathing associated with cardiovascular disease. Theophylline ethylene diamine, 0.48 gram, was injected intravenously in 30 cc of isotonic sodium chloride solution over the period indicated between the arrows. Note the rapid cessation of periodic breathing and the return of normal respiration. (After Greene and Heeren, 1936. Courtesy of the *Waverly Press.*)

Voluntary Muscle. The effect of the xanthines on voluntary muscle is disputed. Although it is agreed that the ingestion of caffeine allays fatigue, there is no unanimity of opinion as to the mechanism of this action. Some investigators believe that it is due to a direct action of the drug on muscles, whereas others claim that central stimulation masks the recognition of fatigue. There are many experimental observations which suggest that the xanthines have a direct action on skeletal muscles. For example, certain species of frogs show marked rigor following the injection of these drugs. The rigor is peripheral rather than central in origin for it is not influenced by nerve section or curare. A definite rigor can be produced in mammalian muscle by injecting a xanthine directly into the muscle. Accompanying this action there is an increase in oxygen consumption and heat production of the muscle. Furthermore, an isolated nerve-muscle preparation is less susceptible to fatigue if a low concentration of a xanthine is present in the bath fluid.

Despite the evidence indicating a peripheral action on skeletal muscle, there is good reason to believe that the central effects of the xanthines account for the increased capacity for muscular work demonstrable in man. The strongest argument in support of this view is the observation that theobromine has the greatest peripheral effect on muscle and yet is relatively ineffective in increasing the capacity for muscular work. Caffeine, on the other hand, is most effective in increasing muscular performance and also has the greatest capacity for stimulating the central nervous system. One may conclude, therefore, that although the xanthines stimulate skeletal muscles under experimental conditions to the extent of rigor, it is the stimulation of the central nervous system which prevents the sense of fatigue and is responsible for the increased capacity for muscular work which follows caffeine consumption.

Diuretic Action. All of the xanthines increase the flow of urine. Theophylline is the most powerful xanthine diuretic but its action is short in duration. Theobromine is slightly less active but its effect is more sustained. Caffeine is the least powerful. A detailed analysis of the mechanism of the diuretic action is given on page 636. The therapeutic uses of the xanthine diuretics are discussed on page 644.

Metabolism. The xanthines, especially caffeine, slightly increase the basal metabolic rate. Numerous investigators have reported that after the ingestion of 0.5 gram of caffeine the basal metabolic rate may increase an average of 10 per cent and occasionally 25 per cent. The maximum change occurs from one to three hours after the administration of the drug. Statistical studies have revealed that the basal metabolic rate of habitual coffee drinkers is slightly higher than normal.

Tolerance. An appreciable degree of tolerance may develop to certain effects of the xanthines, especially the diuretic and vasodilator actions. Cross-tolerance between the members of the group also occurs. No tolerance develops to the central stimulation. Habituation is discussed under caffeine beverages.

Toxicology. The fatal oral dose of caffeine for adults is estimated to be about 10 grams, but no deaths have been reported. Untoward reactions, however, may be observed following the ingestion of one or more grams of caffeine. These are mainly referable to the central nervous and circulatory systems. Insomnia, restlessness and excitement are the earliest symptoms, and may progress to a mild delirium. Sensory disturbances, such as ringing in the ears and flashes of light, are common. The muscles become tense and tremulous. Tachycardia and extrasystoles are frequent and the respiration is quickened. The diuretic action of the drug may be prominent.

If a fatal dose of caffeine is given to animals, central nervous system stimulation proceeds to the convulsive stage. Early in the poisoning, the convulsions are epileptiform in nature; but, as the action of the drug on the spinal cord becomes manifest, they may be replaced by strychnine-like tonic convulsions. Death results from respiratory failure.

The central symptoms of caffeine poisoning may be readily controlled by the administration of depressants of the central nervous system. The short-acting barbiturates are effective and convenient.

Absorption, Fate and Excretion. The xanthines are readily absorbed after oral or parenteral administration. In the case of caffeine, a small portion of the drug is excreted in the urine unchanged or partially demethylated. About 80 per cent of the drug is broken down in the body to urea and not to uric acid, as might be expected. Theobromine and theophylline share the same fate as caffeine except that a slightly larger portion of these drugs may appear unchanged in the urine.

Preparations and Routes of Administration. The xanthines are weakly basic alkaloids. They are usually dispensed in the form of soluble double salts which they form with a number of compounds. For oral administration, either the free base or the double salts may be used. For parenteral administration, however, it is necessary to employ one of the injectable salts.

Caffeine. Caffeine, U.S.P., B.P., is also known as *theine.* It consists of white glistening crystals soluble in water to the extent of 1:46. Two widely employed soluble salts are *Citrated Caffeine,* U.S.P., a mixture of caffeine and citric acid in equal amounts by weight, and *Caffeine with Sodium Benzoate,* U.S.P., B.P., a mixture of equal parts of caffeine and sodium benzoate. For hypodermic administration, the benzoate salt should be used. Both are white water-soluble powders having a slightly bitter taste.

Theobromine. The U.S.P. and B.P. preparation is *Theobromine with Sodium Salicylate,* also known as *diuretin.* It is a white water-soluble powder of sweetish alkaline taste which contains approximately 46 per cent theobromine. In addition, three commonly employed theobromine preparations are included in the N.N.R. They are the free base, *Theobromine,* N.N.R., a white, crystalline, bitter powder slightly soluble in water; *Theobromine Sodium-Acetate,* N.N.R., a white, crystalline, water-soluble bitter powder, which contains not less than 63 per cent theobromine; *Theocalcin,* N.N.R., a mixture of calcium theobromine (44 per cent) and calcium salicylate, which consists of a white amorphous powder having a saline taste and only partly soluble in water. Theobromine preparations may be given only by the oral route.

Theophylline. The commonly employed theophylline preparations are as follows: *Theophylline,* U.S.P., B.P., a white, crystalline, bitter powder soluble 1:120 in water; *Theophylline with Ethylene Diamine* (Aminophylline), U.S.P., a combination containing 70 per cent of theophylline and consisting of white or slightly yellow granules possessing a slight ammoniacal odor and bitter taste, soluble 1:5 in water; *Theophylline with Sodium Acetate,* U.S.P., B.P., which contains 60 per cent theophylline and consists of a white, crystalline, bitter powder soluble 1:35 in water. Theophylline with ethylene diamine is the preparation employed for parenteral administration.

Choice of Preparation. The large number of available xanthines often leads to confusion as to the best preparation to employ. The compounds of caffeine are usually utilized only as central stimulants. Theobromine and theophylline are often used interchangeably for their actions on the coronary circulation and kidney. The choice of preparation is also influenced by the side-actions produced and the cost of medication.

An important side-action is the local effect of xanthines on the gastric mucosa. All preparations are irritating and in therapeutic doses are likely to cause gastric discomfort, nausea and vomiting. Often it is impossible to give the desired amount, and in many instances it is the limit of gastric tolerance which finally determines the dose employed. It is best to give the xanthine drugs after meals in order to reduce the factor of gastric irritation.

Although claims have been made that some salts are less irritating than others to the gastro-intestinal tract, this difference is not sufficiently noticeable to make any one preparation outstanding. The xanthine salts vary considerably in cost (Brown and Riseman, 1937) and this may in part determine the choice of drug when chronic medication is necessary.

Therapeutic Uses. The xanthines are extensively employed as *diuretics.* A detailed discussion of their use in edema appears on page 644.

Another wide use of the xanthines, particularly theophylline and theobromine preparations, is in the treatment of patients with insufficiency of the coronary circulation, as in *angina pectoris.* The vasodilator effect of the xanthines on the coronary arteries has been discussed. Clinical observations have led to the belief that chronic medication with xanthines results in a decrease in the number and severity of anginal attacks. The efficacy of such therapy, however, has been questioned especially by Evans and Hoyle (1933), Gold, Kwit and Otto (1937) and Masters and coworkers (1939). From carefully controlled clinical studies, Gold and Masters and their respective associates came to the conclusion that patients were unable to detect any difference between the effects of xanthines and suitably disguised placebos. On the basis of such findings, the Council on Pharmacy and Chemistry (1937) decided not to accept for inclusion in N.N.R. any xanthine preparation for which claims of therapeutic value in coronary artery disease are made. However, Brown and Riseman (1937) have taken exception to these conclusions. These investigators employed an exercise tolerance test and demonstrated that, although a patient could not distinguish between a xanthine and a placebo on the basis of a subjective analysis of symptoms, he could withstand more physical exertion without experiencing anginal pain after the administration of a xanthine than he could without such medication or after taking a disguised placebo.

Therefore, the status of the xanthines in the treatment of coronary artery disease still remains controversial. When used, the xanthine drugs are given three times daily during meals. The salts may be better tolerated than the free bases. The average single dose of the theophylline compounds is approximately 0.25 gram, of the theobromine salts, 0.6 gram. No statement can be made as to which xanthine salt is most effective. Many physicians give medication for only four days of each week in order to avoid tolerance. It is also a common practice to alternate between a theobromine and a theophylline salt. If gastric disturbance becomes severe, the dosage must be reduced or another preparation tried.

The *direct myocardial stimulation* produced by the xanthines has relatively little therapeutic application. The drugs are not suitable for chronic medication as cardiac stimulants, and more effective agents are available for the treatment of chronic cardiac insufficiency. In *acute circulatory failure,* the xanthines may be of some value, but in the majority of cases the failure is of peripheral rather than cardiac origin. If there is a myocardial element in the circulatory collapse, the parenteral injection of caffeine or theophylline is sometimes beneficial. In patients with *paroxysmal nocturnal dyspnea* due to left ventricular insufficiency, xanthine medication brings relief. In addition to causing cardiac stimulation, the drug relaxes the bronchial musculature, which may further alleviate dyspnea if there is a superimposed factor of bronchospasm. Also, venous and intrathecal pressures are lowered. Theophylline with ethylene diamine is the preparation of choice. It is used in the parenteral dose of 0.25 to 0.50 gram and it may be given intravenously in an emergency.

The *central actions* of caffeine are particularly useful in treating cases of *poisoning by the central depressants.* In morphine poisoning, the direct effect of caffeine on the medulla is of particular value. The drug is given by intramuscular injection as the sodium benzoate salt or by enema in the form of black coffee. The dose of caffeine with sodium benzoate is 0.5 to 1.0 gram.

The xanthines have been used in the treatment of *peripheral vascular disease,* but the results have been disappointing. Scupham (1934) observed some symptomatic relief in cases of early thromboangiitis obliterans, but in general his results were not encouraging. McGovern, McDevitt and Wright (1936) found the xanthines too unreliable and feeble as vasodilators to be of any value in the treatment of peripheral vascular disorders.

In the treatment of *bronchial asthma,* theophylline with ethylene diamine has proved of definite value. The drug is of special benefit in patients refractory to epinephrine. Herrmann and Aynesworth (1937) have reported favorable results in a series of cases of status asthmaticus. The effective dose of 0.25 to 0.50 gram is dissolved in 10 cc of physiological sodium chloride solution and is given slowly intravenously. Favorable responses in bronchial asthma have also been reported following the intramuscular injection of the drug. Oral therapy is usually ineffective in severe or acute attacks, but is useful in mild or chronic cases.

Caffeine has been extensively employed, especially in combination with analgesics and hypnotics, in the treatment of *headache* and *migraine.* The mechanism of action of caffeine in headache may possibly be related to the changes which the drug produces in the cerebral circulation. It is difficult to judge the benefit obtained from caffeine, especially when it is used with other drugs.

XANTHINE BEVERAGES

The most popular of the xanthine beverages are coffee, tea and cocoa. Coffee and tea contain caffeine, whereas cocoa contains theobromine. The caffeine content of tea leaves is higher than that of coffee beans, but the beverages as finally prepared are approximately equal in their alkaloidal content inasmuch as proportionately more coffee is employed. The average cup of coffee contains between 100 and 150 mgm of caffeine, approximately a therapeutic dose. Naturally, the daily ingestion of this amount of a potent alkaloid is bound to exert some pharmacological action. In addition to alkaloids, coffee contains certain oils and tea has an appreciable amount of tannin.

There is little doubt that the xanthine beverages are often consumed for their stimulating action. This probably forms the main basis for their popularity, although most persons are unaware of any stimulation. The xanthine beverages present a medical problem in that they are a dietary source of a stimulant of the central nervous system. Often the physician is faced with the question whether to deny caffeine-containing beverages to patients.

The degree to which an individual is stimulated by a given amount of caffeine varies. It probably is related to what may be termed "individual temperament." For example, if some persons ingest caffeine beverages in the evening, insomnia is almost certain to result. Others boast of their ability to drink coffee and "sleep like a log." Therefore, the degree of action of caffeine is largely influenced by the base line of nervous system irritability. Some individuals are stimulated to a degree that precludes the possibility of adequate relaxation after xanthine beverages. In fact, there are rare persons who are so sensitive to caffeine that even a single cup of coffee will cause a response bordering on the toxic.

Children are more susceptible than adults to xanthine stimulation. Their normal reflex excitability is generally high. What is more, the ingestion of caffeine beverages may interfere with the consumption of necessary foodstuffs. For these reasons, tea and coffee should be excluded from the diet of children. Cocoa, however, which contains theobromine rather than caffeine, may be allowed especially if it is made with milk.

There are certain pathological conditions in which it has been suggested that xanthine beverages be denied to patients. The fact that the xanthines are closely related in structure to uric acid has led to the belief that tea and coffee should be excluded from the diet of patients suffering from gout. However, the methylated xanthines are not excreted as uric acid but rather are broken down to urea, and careful studies have shown that they do not appreciably increase the uric acid content of the urine. Therefore it is doubtful whether on this basis the xanthines could have an adverse effect on podagric individuals.

Often xanthine beverages are denied to individuals with hypertension because of the action of caffeine on the cardiovascular and nervous systems. Obviously in a disease in which sedation is an important factor, stimulation by a xanthine is not to be desired. However, most authorities take the attitude that the complete denial of coffee to an individual who enjoys it is apt to be more disturbing than any stimulation he may receive from the beverage. Again, many patients with hypertension experience neither an increase in blood pressure nor nervousness from xanthine beverages. Indeed, theobromine is frequently prescribed for its renal and perhaps coronary actions in such patients. Xanthine beverages accomplish the same end and in addition may relieve the headache so common in this syndrome. Therefore, coffee and tea are not denied, but their intake may have to be controlled.

Overindulgence in xanthine beverages may lead to a condition which might be considered one of chronic poisoning. Central nervous stimulation results in restlessness and disturbed sleep. Myocardial stimulation is reflected in cardiac irregularities, especially premature systoles, palpitation and tachycardia. The essential oils of coffee may cause some gastro-intestinal irritation, and diarrhea is a common symptom. The high tannin content of tea, on the other hand, is apt to cause constipation.

There is no doubt that a certain degree of psychic dependence (*i.e.*, habituation) develops to the xanthine beverages. This is probably true even of those individuals who do not partake to excess. However, the morning cup of coffee is so much a part of the American dietary that one seldom looks upon its consumption as a drug habit, and there is no evidence that the practice is in any way harmful. The feeling of well-being and increased performance which it affords, although possibly obtained at the expense of decreased efficiency later in the day, is one which few individuals would care to give up

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SECTION IV

LOCAL ANESTHETICS

CHAPTER 18

COCAINE; PROCAINE AND OTHER SYNTHETIC LOCAL ANESTHETICS

THE GENERAL PHARMACOLOGY OF THE LOCAL ANESTHETICS

The local anesthetic drugs are capable of blocking nerve conduction when applied locally to nerve tissue in effective concentration. They exert this effect on any portion of the nervous system and on every type of nerve fiber. For example, the application of a local anesthetic to the motor cortex blocks impulse transmission from that area, and at the other extreme the drug's application to afferent nerve endings prevents the reception of stimuli and transmission of sensory impulses. A local anesthetic in contact with a mixed nerve trunk causes motor and sensory paralysis of the area innervated. The conduction of nerve impulses in the spinal cord may be blocked so completely that cord transection is functionally simulated. The great practical value of the local anesthetic drugs is due to the fact that their action is reversible and is followed by complete recovery of nerve function with no evidence of structural damage to nerve fibers or cells. By the proper use of local anesthetics one can produce sensory and motor paralysis in selected discrete areas with no other effect than the desired local one.

History. The first local anesthetic discovered was cocaine. The alkaloid was isolated in 1860 by Niemann, a pupil of Wöhler. Wöhler noted that cocaine was bitter to the taste and had a peculiar effect on the nerves of the tongue, making it numb and almost devoid of sensation. Von Anrep in 1879 studied the pharmacological actions of cocaine and found that after subcutaneous injection the skin overlying the injected area became insensitive to the prick of a pin. He recommended that this compound might be useful clinically as a local anesthetic. His suggestion was not acted upon, however, and credit for the discovery of local anesthesia is usually ascribed to Sigmund Freud and Karl Köller. A popular story relates that these two investigators were searching for a morphine substitute, and in the course of their studies on cocaine Köller accidentally got some of the drug in his eye and fortunately noted the resulting anesthesia. This story is denied by both principals. The following interesting account of the discovery of local anesthesia appears in Freud's autobiography (1935):

> “In the autumn of 1886 I settled down in Vienna as a physician, and married the girl who had been waiting for me in a distant city for more than four years. I may here go back a little and explain how it was the fault of my fiancée that I was not already famous at that early age. A side interest, though it was a deep one, had led me in 1884 to obtain from Merck some of what was then the little-known alkaloid cocaine and to study its physiological action. While I was in the middle of this work, an opportunity arose for making a journey to visit my fiancée, from whom I had been parted for two years. I hastily wound up my investigations on cocaine and contented myself in my book on the subject with prophesying that further uses for it would soon be found. I suggested, however, to my friend Königstein, the ophthalmologist, that he should investigate the question of how far the anesthetizing properties of cocaine were applicable in diseases of the eye. When I returned from my holiday I found that not he, but another of my friends, Carl Köller (now in New York), whom I had also spoken to about cocaine, had made the decisive experiments upon animals' eyes and had demonstrated them at the Ophthalmological Congress at Heidelberg. Köller is therefore rightly regarded as the discoverer of local anes-

thesia by cocaine, which has become so important in minor surgery; but I bore my fiancée no grudge for her interruption of my work."

The acceptance of cocaine as a local anesthetic was immediate, and in this way the history of local anesthesia differs sharply from that of general anesthesia. Other investigators rapidly extended Köller's initial observation. Within a short time, Hall (1884) introduced local anesthesia into dentistry, and Halsted (1885) by demonstrating that cocaine could block transmission in nerve trunks laid the foundation for block anesthesia in surgery. Corning (1885) produced spinal anesthesia in dogs, but several years passed before this technic was employed in clinical surgery.

Chemical search for cocaine substitutes started in 1892 with the work of Einhorn, and in 1905 this investigator synthesized procaine, which today is more extensively employed than any other local anesthetic. Chemical investigation still continues, however, because no available local anesthetic is free of undesirable properties. As a result an unnecessarily large number of compounds are marketed for clinical use. Most of these differ little in therapeutic efficiency, and few have distinctive features to recommend their use.

Properties Desirable in Local Anesthetics. A good local anesthetic should combine several desirable properties. Obviously it should not be irritating upon local application, and must produce anesthesia without causing damage to nerve structure. Most of the local anesthetics used today fulfill these requirements. The systemic toxicity of a local anesthetic should be low because the compounds are absorbed from their site of local application. The concentration in which a local anesthetic is effective is an important factor to consider in judging the safety of the drug. For example, if the systemic toxicity of two compounds is identical but one requires a higher concentration for local anesthesia, they cannot be considered equally safe in their clinical use. It is clear that the lower the effective anesthetic concentration and the higher the fatal dose, the greater is the margin of safety. In the discussion of barbiturates, it was pointed out that in this series of drugs the toxic and therapeutic doses are proportional and closely parallel each other throughout the series. This does not hold true for the local anesthetics. Compounds equally effective may differ markedly in their toxicity, a fact indicating that the two properties are quite independent. This dissociation of toxicity and potency affords a great stimulus in the search for new, more effective and safer anesthetic agents.

The duration of anesthetic action is another important factor in determining the desirability of a local anesthetic. It must be sufficiently long to allow ample time for the performance of the contemplated surgical procedure. The time required for the onset of anesthesia is likewise important, and should be as short as possible. The ideal local anesthetic also is one which is effective regardless of the locus of administration. It should be active when injected or when applied locally to mucous membranes.

There are excellent laboratory procedures available for testing the factors discussed, and the choice of suitable agents for clinical trial is largely determined by the results obtained from such tests. The laboratory data for several of the more commonly used local anesthetics are presented in Table 15.

General Properties of Local Anesthetic Drugs

The local anesthetics as a group have many actions in common, and before discussing the pharmacology of the individual members these general properties will be considered.

Mechanism of Action. Little is known of the mechanism of action of the local anesthetics. It has been postulated that they act in the same basic manner as general anesthetics, the main difference being that a higher concentration of local anesthetic is necessary. According to this view, local anesthetics are not active after systemic administration because death occurs from medullary depression before the higher centers are anesthetized. There is little evidence in support of this theory.

Despite the paucity of information concerning the mechanism of local anesthesia, it is known that certain nerve fibers are more susceptible than others to the action of this group of drugs. Thus it has been found that in a mixed nerve the sensory fibers are blocked earlier than the motor. In fact, when the proper concentration of anesthetic is applied to a nerve, it is possible to block completely the sensory fibers without abolishing the transmission of motor impulses. Also, it has been established that there is a definite order in which the fibers in a sensory nerve are affected by local anesthetics. The sensation of pain is the first modality to disappear and it is followed in order by the sensations of cold, warmth and touch. Various theories have been presented to explain this difference in susceptibility. For a long time it was thought that the phenomenon was due to a difference in the chemical constitution of the fibers. Gasser and Erlanger (1929), however, were impressed with the fact that when pressure is applied to a mixed nerve the resulting anesthesia of the motor and sensory fibers appears in a sequence opposite to that observed after block by anesthetic drugs, namely, the motor fibers are affected before the sensory. They demonstrated by the use of the cathode ray oscillograph that fiber size is the main factor in determining the relative sensitivity to pressure and to chemical anesthesia. After cocaine is applied to a mixed nerve, the gamma waves (from small cutaneous afferent fibers) are the first and the alpha waves (from large fibers) the last to disappear. Inasmuch as cocaine probably acts by chemical combination with the nerve protoplasm, it is logical that the smaller fibers which present the greatest surface per unit of volume are the first to be anesthetized. This concept receives support from the observation that if a local anesthetic is applied to the vagus nerve, the smaller efferent cardioinhibitory fibers are blocked before the larger fibers which carry afferent respiratory impulses.

Action on the Myoneural Junction and Ganglionic Synapse. The actions of local anesthetics are not confined to nerve trunks and fibers but apparently affect synaptic transmission as well. Harvey (1939) has studied the effects of procaine on synaptic transmission in the light of the newer knowledge of the chemical mediation of the nerve impulse (page 323). He prepared decerebrate cats for close intra-arterial injection of the tibialis anterior muscle and observed that the intra-arterial injection of as little as 0.2 mgm of procaine reduced the tension of muscle twitches evoked by maximal motor nerve volleys delivered at 10-second intervals. The response to tetanic stimulation was also impeded, but the muscle responded normally to direct electrical stimulation. That the effect of the local anesthetic was not solely on the motor nerve endings was shown by the fact that the response of the muscle to injected acetylcholine was blocked. The actions of procaine and physostigmine were antagonistic; of procaine and curare, additive. There was no stimulatory phase to the action of procaine on muscle and in every way it could be likened to that of curare.

Similarly if procaine was added to the fluid perfusing a ganglion, ganglionic transmission was impeded. Preganglionic stimuli failed to elicit postganglionic discharges and the ganglion cells became insensitive to stimulation by acetylcholine. That procaine, however, had a marked effect on synaptic endings of preganglionic fibers as well as on ganglion cells was shown by the fact that the production of acetylcholine in response to preganglionic stimulation was diminished. In this respect the actions of procaine and curare differ.

Potentiation by Alkali. The local anesthetics are generally marketed in the form of their water-soluble acid salts, usually the hydrochlorides. There is evidence to show, however, that it is the free base which acts on nerve tissue. In their basic form, the local anesthetics are lipid-soluble. In fact, to a certain extent they obey the Meyer-Overton law (page 32). It is highly probable that the free base is liberated in the tissues by the slightly alkaline body fluids. Most of the local anesthetics are tertiary amines, and the reaction which takes place in the tissues may be simply illustrated as follows:

$$\underset{\text{Acid Salt}}{R\vdots N\cdot HCl} + NaHCO_3 \longrightarrow \underset{\text{Free Base}}{R\vdots N} + NaCl + H_2CO_3$$

It is possible to demonstrate that the addition of alkali to anesthetic solutions increases, to some extent, their anesthetic potency. After alkalinization, however, the solutions become turbid, and the free base may separate out. As a practical therapeutic procedure, therefore, alkalinization of anesthetic solutions is seldom employed. Rather one relies on the ability of tissue fluids to liberate the active base. In extreme conditions, when the anesthetics encounter an acid reaction in tissues, as in acutely infected areas, it is difficult to produce local anesthesia.

A certain amount of the free base is liberated by the spontaneous hydrolysis of a local anesthetic salt in aqueous solution. The extent of hydrolysis is influenced by the strength of both the acid and base portions of the molecule. When the local anesthetic is present as the salt of a strong acid, *i.e.,* a hydrochloride, spontaneous hydrolysis is at a minimum. The salts of weak acids, however, hydrolyze more readily. In an attempt to take practical advantage of this physical property, boric acid salts of local anesthetics have been marketed. Presumably the liberation of the free base is facilitated. Although an increased efficiency can be demonstrated in the laboratory, it is not of sufficient magnitude to be of clinical significance. Again, there is evidence that the degree of basicity of the free anesthetic alkaloid influences the rate of spontaneous hydrolysis of its salts and has a marked effect on anesthetic potency. Thus the less basic alkaloids are more active inasmuch as their salts hydrolyze more readily to yield the active free base.

Potentiation by Epinephrine. The duration of action of local anesthetics is proportional to the time during which they are in actual contact with nervous tissue. Consequently procedures which localize the drug at the nerve greatly prolong the period of anesthesia. Cocaine itself constricts blood vessels and therefore prevents its own absorption. For this reason, the duration of cocaine anesthesia is greater than that of most anesthetics which do not cause vasoconstriction. Braun in 1903 demonstrated that the addition of epinephrine to local anesthetic solutions greatly prolongs and intensifies their action. In clinical practice, therefore, the injection of a local anesthetic is usually accompanied by epinephrine or one of its suitable synthetic congeners. A concentration of 1:25,000 to 1:50,000 of epinephrine hydrochloride is sufficient for this purpose. The epinephrine performs a dual service. By decreasing the rate of absorption epinephrine not only localizes the anesthetic agent at the desired site but also allows the rate at which the anesthetic is destroyed in the body to keep pace with the rate at which it enters the circulation. Thus a toxic concentration is not reached.

Fate of Local Anesthetics. All the local anesthetics are destroyed by the liver. The rate at which they are destroyed, however, varies greatly and this is a major factor in determining the safety of a particular anesthetic agent. In practical use, the toxicity of a local anesthetic depends upon the ratio between the rate of absorption and the rate of destruction. As has already been stated, the rate of absorption of all the anesthetic agents can be reduced nearly to a common base line by the incorporation of epinephrine in the anesthetic solution. With respect to rate of destruction, Eggleston and Hatcher (1919) showed that the local anesthetics can be divided into two groups, those rapidly and those slowly detoxified.

One minimal lethal dose of a member of the first group can be detoxified by the body in 20 minutes, whereas 60 minutes are required for the slowly detoxified local anesthetics. The speed with which the liver can detoxify different local anesthetics is one of the chief reasons for their varying toxicities.

There is abundant proof that the liver is the site of destruction of the local anesthetics. These drugs lose their toxicity after perfusion through the liver, probably as the result of hydrolysis. Also animals with experimentally produced liver damage are much more susceptible to the toxic actions of local anesthetics. This suggests that extensive use of a local anesthetic should perhaps be avoided in patients with severe liver damage. Those anesthetic agents which are slowly destroyed by the liver are partially eliminated in the urine but only a small fraction is normally excreted by the kidney.

Toxicity of Local Anesthetics. *Central Nervous System.* There is a wide variation in the lethal doses of the various local anesthetics. The degree of toxicity does not always parallel the degree of anesthetic activity, and there apparently need be no obligatory relationship between the two. On the other hand, it is highly significant that all the local anesthetics produce the same type of symptoms when given in toxic amounts. These symptoms, mainly referable to the central nervous system, result from central stimulation and consist chiefly of restlessness and tremors which proceed to clonic convulsions. Stimulation is followed by depression and death is usually due to respiratory failure. In fact, it is possible to protect animals from two to three times the minimal lethal dose of a local anesthetic by the use of artificial respiration (Tatum, Atkinson and Collins, 1925). Attempts have therefore been made to use respiratory stimulants as antidotes against the toxic effects of local anesthetics. Such procedures have proved ineffective, however, for the reason that the local anesthetics in themselves are central nervous system stimulants, and the eventual depression of the respiratory center which they produce is that which characteristically follows excessive stimulation.

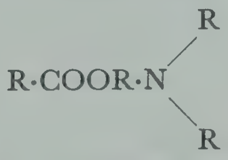
Tatum, Atkinson, and Collins (1925) pointed out that the logical drugs to use in the prevention and treatment of poisoning by local anesthetics are the hypnotics. Of this group, they found that the barbiturates are the most valuable. Not only are the barbiturates effective in arresting convulsions resulting from an overdose of local anesthetic but if given prophylactically the minimal lethal dose of the local anesthetic is increased three or four times. The practical importance of these observations is mentioned under the clinical use of the local anesthetics. Different species of animals vary in susceptibility to central stimulation by local anesthetics, and seemingly this is related to the degree of development of the central nervous system. Thus the higher forms, such as monkey and man, are much more sensitive to the toxic action of these drugs. Tatum and Collins (1926) showed that the barbiturates afford the higher species relatively more protection.

Whereas all the local anesthetics stimulate the central nervous system, cocaine is unique in having a powerful action on the cortex. This property of cocaine and its ability to produce addiction will be discussed later. The synthetic local anesthetics, in contrast, are less stimulating to the higher cerebral centers and are incapable of causing addiction.

Cardiovascular Actions. In addition to their toxic effect on the central nervous system the local anesthetics may act adversely on the circulatory system. Cocaine has the most pronounced action and the synthetic local anesthetics are variable in this respect. Upon intravenous injection, some may produce a slight rise in blood pressure; others, a fall. These slight alterations in blood pressure are usually unimportant. On rare occasions, however, the administration of relatively small amounts of a local anesthetic may result in sudden cardiovascular collapse and death. This untoward reaction must be classified as an idiosyncrasy for it occurs rarely and bears no relation to dosage. Some of the toxic manifestations following the administration of local anesthetic solutions are due to sensitivity to epinephrine. Reactions to epinephrine are not uncommon.

A unique action of local anesthetics, particularly procaine, is their ability to reduce the irritability of heart muscle to noxious stimuli of an electrical or chemical nature. Mautz (1936) showed that the local application of anesthetics to the ventricular muscle raised the threshold for the induction of ventricular extrasystoles by electrical stimulation. Of even greater interest is the fact that the intravenous administration of procaine protects animals anesthetized by cyclopropane from the ventricular fibrillation which can be induced by epinephrine (Burstein and Marangoni, 1940) and that the intracardiac injection of procaine can stop fibrillation that has already become established (Marangoni, Burstein and Rovenstine, 1940). The mechanism of this action has not been determined.

Chemistry of Local Anesthetics: Relationship Between Constitution and Action. The pharmacological activity of most synthetic local anesthetics apparently resides in a certain basic structure. Inspection of the structural formulas of the individual anesthetics reveals that they are tertiary amino esters of aromatic acids. This fundamental structure may be represented as follows:

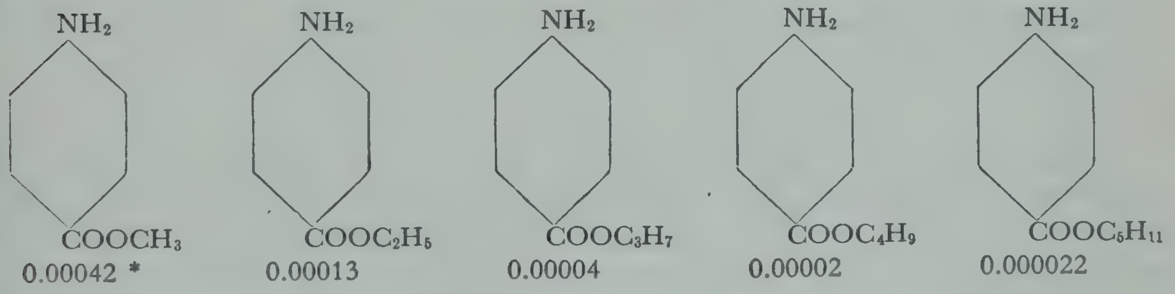


$$R\cdot COOR\cdot N\begin{matrix} R \\ R \end{matrix}$$

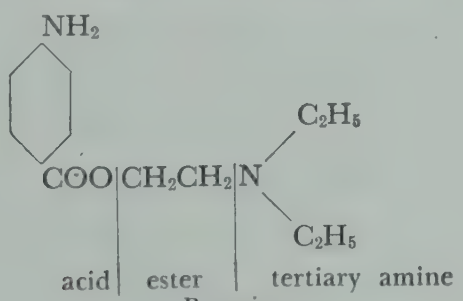
The tertiary amine is not essential for anesthetic action because simple esters are effective. Thus the esters of amino benzoic acid have the property of producing local anesthesia. In the series of esters depicted in Table 14, anesthetic activity increases with the length of the ester chain (Adams and coworkers, 1926). These particular compounds, however, are quite insoluble and their use is limited. If a tertiary amino group is introduced into the ester portion of the molecule, a more basic substance is obtained which forms soluble acid salts. For example, when a diethyl amino group is added to the ester chain of para-amino ethylbenzoate, the second compound shown in Table 14, the well-known anesthetic procaine is obtained. The structures of procaine and one of its soluble acid salts, the hydrochloride, are as follows:

Table 14

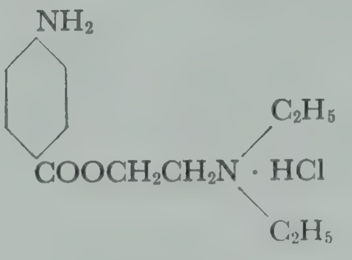
THE EFFECT OF LENGTHENING THE ESTER CHAIN ON ANESTHETIC ACTIVITY



* Minimal anesthetic concentration in mols.
Adams and associates, 1926.

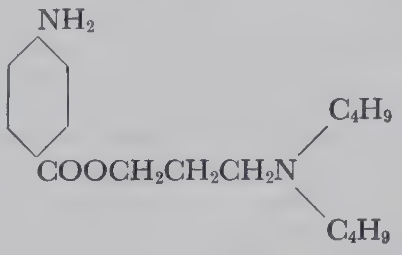


Procaine



Procaine Hydrochloride

It is evident that the procaine molecule can be divided into three main portions—the acid, the ester, and the tertiary amino group. Changes in any part of the molecule alter the anesthetic potency and the toxicity of the compound, and have led to the vast number of available local anesthetics. For example, if in procaine there is merely added one carbon atom to the ester group to form a propyl ester, and the amino group is changed from diethyl to dibutyl amine, the resulting compound is butyn, an anesthetic which is more potent, but more toxic than procaine.



Butyn

Certain general conclusions have been drawn with respect to the relationship between changes in chemical structure and pharmacological activity. Increasing the length of the ester group leads to an increase in toxicity, and thus compounds with an ethyl ester, such as procaine, exhibit the least toxicity. Concomitantly, increasing the length of the ester group decreases the basicity of the compound. As has already been explained, this leads to a more rapid liberation from the acid salt of the active free base, and therefore to a greater anesthetic potency. Also, an increase in length of the groups on the tertiary amino nitrogen decreases basicity. Both types of change have been made in the transition from procaine to butyn, and this accounts for the marked increase both in activity and toxicity of butyn as compared with procaine (Table 15).

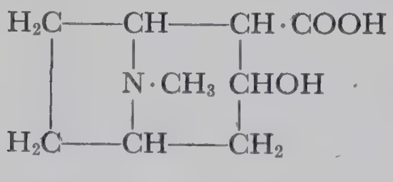
The number of compounds which conceivably could have anesthetic activity is almost infinite. Not only esters, but also ethers and amides (*see* structure of nupercaine) often exhibit this pharmacological property. The foregoing discussion merely indicates the procedures available to the chemist in exploring this fascinating field.

THE PHARMACOLOGY OF THE INDIVIDUAL LOCAL ANESTHETICS

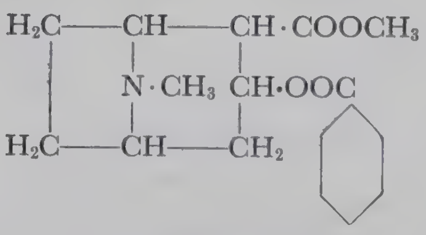
Cocaine

Source. Cocaine is obtained from the leaves of the *Erythroxylon coca* and other species of *Erythroxylon.* The tree is indigenous to Peru and Bolivia where its leaves have been used for centuries by the natives, not so much for local anesthesia as for stimulation of the central nervous system, since cocaine possesses both these properties. The native Indian runners chew the leaves in order to lessen hunger (local action on the gastric mucosa) but mainly to increase endurance (central stimulation).

Chemistry. Cocaine is benzoyl methylecgonine. Ecgonine is a base closely related to tropine, the base of atropine. Cocaine is thus an ester of benzoic acid and a nitrogen-containing base and has the fundamental structure previously described for the synthetic local anesthetics. The structural formulas of ecgonine and cocaine are as follows:



Ecgonine



Cocaine

Pharmacological Actions

The important clinical action of cocaine is its ability to block nerve conduction upon local application. Its most striking systemic effect is stimulation of the central nervous system. In addition cocaine has numerous important side-actions.

Central Nervous System. Cocaine stimulates the central nervous system from above downward. The first recognizable action is on the cortex. In man, this is manifest in garrulity, restlessness and excitement. There is some evidence that mental powers are increased. There may also be an increased capacity for muscular work probably due to a lessened sense of fatigue. Sir Arthur Conan Doyle's famous Sherlock Holmes took advantage of the central effects of cocaine, much to the perturbation of Dr. Watson. Other effects on the cerebral cortex are discussed under cocaine addiction. In animals, the cortical action is manifested mainly by increased motor activity. After small amounts of cocaine, motor activity is perfectly coordinated, but as the dose is increased the lower centers also are affected. Stimulation of lower motor centers causes tremors and convulsive movements. Cord reflexes are increased and eventually clonic and tonic convulsions appear.

The action of cocaine on the medulla results in an increase in the respiratory rate. At first the depth of respiration is unaffected but soon it is diminished so that breathing is rapid and shallow. The vasomotor and vomiting centers may also share in the stimulation, and emesis is not uncommon.

Central stimulation is soon replaced by depression. The higher centers are the first to be depressed and this may occur when the lower portions of the cerebrospinal axis are still in the stage of excitation. Thus unconsciousness and convulsions may coincide. Eventually the vital medullary centers are depressed and death results from respiratory failure.

Cardiovascular System. Small doses of cocaine may slow the heart rate as a result of central vagal stimulation. After moderate dosage, however, the heart rate is definitely increased. Tachycardia has been ascribed to vagal paralysis, but the explanation is doubtful inasmuch as vagal stimulation is still effective in slowing the heart. The increased cardiac rate probably results from increased sympathetic stimulation of both central and peripheral origin, although cocaine may also stimulate the myocardium directly. The administration of a large intravenous dose of cocaine may result in immediate death from cardiac failure due to a direct toxic action on heart muscle. Vasoconstriction due to central vasomotor stimulation, coupled with tachycardia, causes a prominent increase of blood pressure. Later the blood pressure may fall. On local application, sufficient cocaine reaches the blood vessels to cause direct vasoconstriction; but after the systemic administration of the drug, the vasoconstriction is central in origin because section of the spinal cord prevents the vascular response.

Skeletal Muscle. The relief of fatigue by cocaine has led to an investigation of the effect of the alkaloid on voluntary muscle. There is no evidence that cocaine increases the strength of muscular contraction. Therefore, it must be concluded that the ability of the drug to relieve or delay fatigue results from central stimulation which masks the sensation of fatigue.

Body Temperature. Cocaine is a marked pyretic. Three factors contribute to raise body temperature. The increased muscular activity attending stimulation by cocaine augments heat production. Vasoconstriction due to central vasomotor stimulation decreases heat elimination. Lastly there is reason to believe that cocaine has a direct action on the heat regulating centers, for the onset of cocaine fever is often heralded by a chill which is an indication that the body is adjusting its temperature to a higher level. Cocaine pyrexia is often a striking feature of cocaine poisoning, and may easily be elicited in animals by sub-lethal doses.

Sympathetic Nervous System. Cocaine has the property of potentiating the responses of sympathetically innervated organs to epinephrine, sympathin, and to sympathetic nerve stimulation. Cocaine potentiation was first observed by Frölich and Loewi in 1910, and many explanations have since been offered to account for the phenomenon. It seems well established that cocaine does not have a direct stimulating or nonspecific sensitizing action on sympathetically innervated structures, as is indicated by the lack of response to cocaine upon denervation of the effector cells. Also, cocaine potentiates both excitatory and inhibitory responses of muscles and glands to epinephrine or adrenergic nerve impulses, and it is difficult to understand how cocaine, by acting directly on the effector cells, can augment such variegated types of response. It has been suggested that cocaine enhances the production of sympathin, but this does not account for the fact that the action of injected epinephrine is potentiated. Two explanations of the sympathomimetic property of cocaine offered by Cannon and Rosenblueth (1937) which apparently can be reconciled with experimental findings are: (1) Cocaine may prevent the destruction of injected epinephrine or of sympathin, or (2) cocaine may increase the permeability of sympathetically innervated cells and thus favor the entrance of the stimulating agent. The experimental evidence of Philpot (1940) that cocaine inhibits amine oxidase, the enzyme concerned with the oxidation of epinephrine, favors the first explanation.

Local Actions. The most important local action of cocaine is its ability to block nerve conduction when brought into direct contact with nerve tissue. Cocaine blocks terminal sensory nerve fibers in a concentration as low as 0.02 per cent. Higher concentrations are required to block conduction in nerve trunks or to produce anesthesia by direct contact with mucous membranes (Table 15).

Cocaine is a "general protoplasmic poison." There is no reason to believe, however, that cocaine produces anesthesia by virtue of this property. The concentration of cocaine which is effective as an anesthetic does not damage cells. Furthermore, other local anesthetics structurally similar to cocaine do not share its toxic effect on protoplasm. The action of cocaine on protoplasm is manifest in the ability of the drug to arrest the motility of ciliated epithelial cells, leukocytes, spermatozoa, and similar unicellular structures. Putrefaction may also be delayed by cocaine.

Eye. The local action of cocaine on the eye is of particular importance because cocaine is often applied to this organ. Anesthesia of the cornea follows contact with solutions of 0.25 to 0.5 per cent. There is an accompanying constriction of the conjunctival vessels and the sclera is blanched. Anesthesia may extend to the iris. Mydriasis also occurs. The mechanism of the mydriatic action of cocaine is not understood. The pupil of the cocainized eye responds to light, and pilocarpine and physostigmine still produce miosis. If the action of atropine is superimposed on that of cocaine, further mydriasis occurs. The reverse is also true, namely, that cocaine enhances the mydriatic action of atropine. These facts are not compatible with the view that cocaine depresses the sphincter muscle of the iris. Rather mydriasis seems to be explainable on the basis of the sympathomimetic action of cocaine.

Cocaine in high concentration is capable of causing cycloplegia. The loss of accommodation is only partial, however, with concentrations used for corneal anesthesia. Cocaine has varying effects on intraocular pressure. In most instances it causes a reduction of intraocular pressure through vasoconstriction. Occasionally, however, the application of cocaine to the eye precipitates an attack of acute glaucoma. It is believed that the mydriasis may cause mechanical block of drainage from the anterior chamber.

In concentrations usually employed for anesthesia, cocaine has a deleterious effect on the cornea. The cornea may become clouded, pitted, and ulceration occasionally follows. This toxic action of cocaine is usually enhanced by the fact that the normal protective eyelid reflexes are abolished by the anesthesia of the cornea. The cornea may become dry and contaminated with foreign material. For this reason, the conjunctival sac is kept well irrigated with physiological salt solution during operations on the cocainized eye.

It is obvious that there are many properties of cocaine which detract from its value as a local anesthetic in ophthalmology. The two main drawbacks are the mydriasis and the corneal injury which it produces. Consequently cocaine has been largely replaced in this field by synthetic anesthetic agents which will be discussed.

Absorption, Fate and Excretion. The vasoconstriction occurring upon the local application of cocaine limits the rate of absorption of the anesthetic. Despite this fact, the rate of absorption may easily exceed the rate of detoxification and excretion. Consequently cocaine can be highly toxic. Cocaine is absorbed from all sites of application including mucous membranes. Absorption even occurs from the urinary bladder, especially in the presence of inflammation. When given orally, cocaine is largely hydrolyzed in the gastro-intestinal tract and rendered ineffective.

After absorption, cocaine is detoxified by the liver. It has been estimated that the liver can detoxify one minimal lethal dose of cocaine in 60 minutes. Some of the drug may be excreted unchanged in the urine. Although cocaine is destroyed much more rapidly than most alkaloids, its rate of detoxification is exceeded by many of the synthetic local anesthetics. Therefore it is more toxic after subcutaneous administration than are many of its substitutes.

Tolerance and Addiction. Cocaine is a powerful cortical stimulant and is indulged in licentiously by certain individuals to elicit this effect. Clinically, cocaine is not employed as a central nervous system stimulant because it is much too toxic for this purpose. In the discussion of morphine addiction, it is pointed out that the addict takes morphine mainly to keep free from withdrawal symptoms and to remain normal. This is not true of the cocaine addict. Cocaine causes euphoric excitement, and pleasurable hallucinations add to the satisfaction obtained. There is a feeling of great muscular and mental strength and the addict greatly overestimates his capabilities. The cocaine addict is not a normal individual but is often a dangerous and debased person. Many addicts become paranoid and suffer from ideas of persecution. As a result, they may carry firearms which they do not hesitate to use. The addict believes that he is being threatened, and that his thoughts are being read by others. Auditory, visual and tactual hallucinations are not uncommon. Black spots are seen on light backgrounds and are mistaken for insects. The sensation of something alive crawling under the skin (formication) is a common complaint. In addition to mental deterioration, the cocaine addict may experience digestive disorders, nausea, loss of appetite, emaciation, sleeplessness, tremors, and occasional convulsions.

The local actions of cocaine are prominent. If the drug is taken by subcutaneous injection, abscesses are common and multiple scars at the sites of injection may serve to identify a cocaine addict. These abscesses are the combined result of prolonged ischemia due to vasoconstriction by cocaine, protoplasmic toxicity of the alkaloid, and infection from lack of sterile technic. Many addicts take the drug by snuffing, utilizing the mucous membranes of the nose as a route of absorption. Cocaine powder is used for this purpose and is commonly called "snow." The nasal septum may occasionally be perforated due to prolonged vasoconstriction and the toxic action of cocaine.

The continued use of cocaine leads to a certain degree of tolerance. Tolerance to cocaine usually is not as marked as that which develops to morphine. Nevertheless, there have been reports of individuals taking as much as 10 grams of cocaine daily. The mechanism of tolerance to cocaine is unknown. It clearly differs from that to morphine in that it cannot be produced in laboratory animals. Psychic dependence on cocaine (habituation) is marked but physiological dependence (addiction) is not as clearly demonstrable as in the case of morphine addiction. Indeed, some investigators claim that addiction to chemicals other than the phenanthrene derivatives of opium has not been satisfactorily demonstrated. At any rate, addiction to cocaine is not as severe as that to morphine, and hence the abstinence syndrome is less marked and withdrawal less difficult.

In treating the cocaine addict, the drug should be withdrawn immediately rather than gradually, and treatment is essentially the same as that employed in morphine withdrawal. The patient suffers from severe depression, and delusions may persist for several weeks. Most cocaine addicts are psychopathic individuals and personality and environmental readjustment is as essential as medical therapy.

Acute Cocaine Poisoning. Due to the wide use of cocaine as a local anesthetic, acute poisoning from cocaine is not rare. This is largely the result of considerable individual variation in susceptibility to the drug. The fatal dose has been stated to be 1.2 grams, obviously only an approximate figure. Severe toxic effects have been reported from doses as low as 20 mgm.

The symptoms of cocaine poisoning are mainly referable to the central nervous system. The patient quickly becomes excited, restless, garrulous, anxious and confused. Reflexes are hyperactive. Headache is common. The pulse becomes rapid and the respirations irregular. A chill may herald the onset of a sudden rise in temperature. The pupils are dilated and exophthalmos occurs. Nausea, vomiting and abdominal pain are frequent. The disturbance in cutaneous sensation described under cocaine addiction also appears. Delirium, Cheyne-Stokes respiration, convulsions and unconsciousness occur terminally. Death results from respiratory arrest. Acute poisoning by cocaine runs a very rapid course. Indeed, there is a form of acute cocaine intoxication which results in almost immediate death, the patient often collapsing and dying before the physician realizes what has occurred. This type of poisoning probably results from rapid absorption of a high concentration of cocaine which is toxic to the heart.

Treatment. The specific treatment of acute cocaine poisoning is the intravenous administration of a relatively short-acting barbiturate. The intravenous route is necessary because symptoms progress with great rapidity. The same principles of dosage apply as those for the therapy of strychnine poisoning. Artificial respiration may be necessary. An important consideration is to limit absorption of the drug. The circulation from the site of cocaine absorption should be stopped by a tourniquet or in any other way possible. If the entrance of the drug into the circulation can be checked and respiratory exchange maintained, the prognosis is favorable because cocaine is destroyed fairly rapidly. There is no effective therapy for the type of cocaine poisoning characterized by sudden cardiovascular collapse and death. The *prophylaxis* of untoward responses to cocaine is discussed under the clinical uses of local anesthetics.

Preparations and Doses. *Cocaine*, U.S.P., B.P., and *Cocaine Hydrochloride*, U.S.P., B.P., are the official preparations of the alkaloid. Both are white crystalline powders. The alkaloidal base is freely soluble in organic solvents; the hydrochloride salt, in water. Cocaine is not used internally or injected. Solutions employed clinically for surface anesthesia vary from 1.0 to 4.0 per cent (cornea) to 10 to 20 per cent (nose and throat), depending on the mucosal surface being anesthetized. Epinephrine is usually incorporated in these solutions. Occasionally, dry cocaine powder is moistened with epinephrine solution to form so-called "cocaine mud" for use on the nasal mucosa, but this practice may be dangerous.

Cocaine, because of its addicting potency, is included among the drugs whose use is controlled by the Federal Narcotic Regulations.

SYNTHETIC LOCAL ANESTHETICS

The number of synthetic local anesthetics is so large that it is impossible to consider all of them. Therefore, a discussion of the individual members of this series will be limited to those which are official in the U.S.P. or have been accepted by the Council on Pharmacy and Chemistry for inclusion in the N.N.R. These sources provide a wide range from which the physician may select anesthetics for any specific purpose.

Procaine

Procaine was synthesized by Einhorn in 1905 and introduced under the trade name *novocaine*. It is probably the most important of all local anesthetics. The chemical structure of this drug has been discussed. Procaine is only one-quarter as toxic as cocaine either after intravenous or subcutaneous administration (Table 15), despite the fact that procaine is destroyed much more rapidly than cocaine in the body. After intravenous injection, the lethal dose of a drug bears no predict-

TABLE 15

LABORATORY DATA ON REPRESENTATIVE LOCAL ANESTHETICS

	THRESHOLD ANESTHETIC CONCENTRATIONS			DURATION OF ANESTHESIA			TOXICITY RABBITS	
	(1) %	(2) %	(3) %	(4) Min.	(5) Min.	(6) Min.	(7) Mgm/Kg	(8) Mgm/Kg
Procaine	0.250	4.0	0.04	0–2	16	171	460	55
Butyn	0.125	0.31	0.02	30	45	200	50	12
Nupercaine	0.004	0.003	0.0025	51 *	100	221	10	2.5
Cocaine	0.125	0.32	0.02	22	12	200	126	15

(1) Frog Sciatic Nerve-Sensory Block
(2) Rabbit Cornea
(3) Intracutaneous Wheal-Human
(4) Rabbit Cornea — 1% solution
(5) Human Intracutaneous — 0.5%
(6) Human Intracutaneous — 0.5% + Epinephrine 1:50,000
(7) Subcutaneous M.L.D.
(8) Intravenous M.L.D.

* 0.1% solution.

able relationship to the rate of destruction because a fatal concentration is immediately reached in the body. After subcutaneous administration, however, the attainment of toxic blood levels depends upon both the rate of absorption and destruction. Therefore, on the basis of rate of destruction, one would expect the ratio of the toxic doses of procaine and cocaine to be much greater after subcutaneous than after intravenous administration. One must remember, however, that cocaine causes vasoconstriction and is therefore slowly absorbed, whereas procaine lacks this property and gains more rapid access to the circulation. If absorption is slowed, the toxicity of procaine is greatly decreased, for procaine is rapidly destroyed by the liver, In clinical use, procaine is always administered in combination with epinephrine. In this manner its absorption is delayed, and toxic reactions are rare.

Clinical Uses. Unfortunately procaine has a limited field of usefulness as a local anesthetic. It has poor penetrating power and therefore is not serviceable for application to mucous membranes. For example, a four per cent concentration of procaine is necessary to produce minimal anesthesia of the cornea. If procaine is applied to mucous membranes, a high concentration (10 to 20 per cent) must be employed. Obviously this is an expensive procedure, and for surface anesthesia there are more effective agents. For this reason, procaine is mainly employed for injection anesthesia. The concentration used for infiltration is usually 0.25 to 0.5 per cent. For nerve block, a one or two per cent solution is commonly employed, the lower concentration being adequate for most purposes. Obviously, one should use the smallest amount of anesthetic solution compatible with successful anesthesia. A total injection of 0.5 gram of procaine during the course of a surgical procedure is a conservative amount, as for example, 50 cc of a one per cent solution. As much as three grams have been employed in a single operation without untoward symptoms.

Toxicity. Although procaine is the least toxic of all local anesthetics, it sometimes causes systemic effects in unusually sensitive individuals. Deaths have been reported from the injection of as little as 0.01 to 0.13 gram of procaine. Such responses are probably due to idiosyncrasy and fortunately are rare. Death is usually characterized by cardiovascular collapse and occurs immediately following the administration of procaine. Some individuals are extremely susceptible to the central nervous system stimulation which procaine may produce. The reaction is slow in onset and can be completely controlled by the use of barbiturates.

Preparations. Procaine is available in the form of three salts—the hydrochloride, borate, and nitrate. Only the hydrochloride salt is official in the U.S.P. and B.P., the other two being N.N.R. preparations. These salts are practically identical in action. A point to bear in mind is the fact that the borate radical so increases the molecular weight of the compound that the concentration employed must be increased by 50 per cent. Procaine is marketed with or without epinephrine in a wide range of doses and concentrations. It is dispensed in ampules as dry white crystals or in solution, and in tablet and powder form.

Butyn

Butyn, N.N.R., is closely related chemically to procaine, being the dibutylaminopropyl ester of para-aminobenzoic acid. Its action as an anesthetic agent, however, may be more closely compared with that of cocaine.

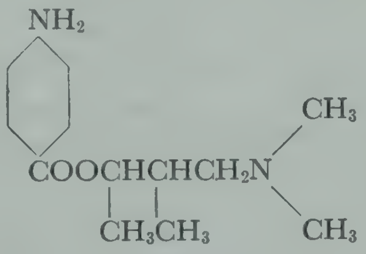
After intravenous injection, cocaine and butyn have the same toxicity. After subcutaneous administration, butyn is the more toxic (Table 15). This is probably due to the fact that cocaine is more slowly absorbed rather than that butyn is more difficult to destroy. The anesthetic potency of butyn is practically the same as that of cocaine. Butyn penetrates mucous membranes readily, and its chief use is to produce surface anesthesia. Its high toxicity contraindicates its employment in procedures requiring injection of the anesthetic.

Butyn has largely replaced cocaine as a surface anesthetic inasmuch as it possesses most of the advantages and few of the disadvantages of cocaine. For example, it has good penetrativeness, rapid onset of action and long duration of anesthesia. When applied to the eye it neither causes ischemia nor affects the pupil. The absence of mydriasis is an advantage of considerable importance in operations on the iris. Butyn is also less damaging than cocaine to the cornea.

For surface application butyn is usually used as the sulfate salt in a two per cent solution. It is also employed in an ointment base for local application to the eye. Although butyn is occasionally injected, its high toxicity makes such a procedure dangerous. Safer agents are available for injection anesthesia.

Tutocaine

Tutocaine, N.N.R., is another ester of para-aminobenzoic acid and a tertiary amino base. It has the following structural formula:

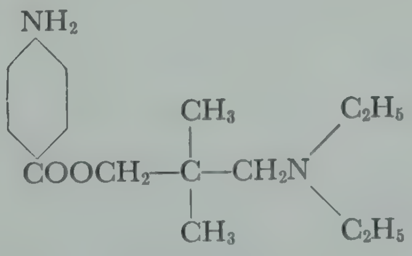


Tutocaine

Tutocaine is slightly less toxic than cocaine after intravenous injection and less than half as toxic as cocaine after subcutaneous administration. It is comparatively safe for injection anesthesia inasmuch as concentrations of 0.2 per cent are anesthetic. It is effective after topical application, and for use in the eye a one per cent solution is sufficient. Two to five per cent solutions are used to produce anesthesia of the nose and throat and it is claimed that the higher concentration shrinks the mucous membrane. For application to the urethra, the recommended concentrations range from one-half to two per cent depending upon the nature of the surgical procedure. It is available as the hydrochloride salt.

Larocaine

Larocaine, N.N.R., is another member of the procaine family of local anesthetics, being a tertiary amino ester of para-aminobenzoic acid. Its structural formula is as follows:

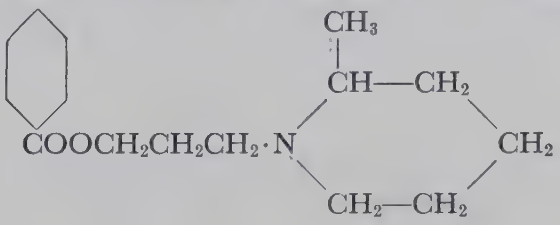


Larocaine

Larocaine is active both as a surface and an injection anesthetic. It is twice as potent as cocaine on the eye and has none of the undesirable effects of the latter. It also has a longer duration of action. When compared with procaine, larocaine is more active as a block anesthetic. However, it is as toxic as cocaine upon intravenous administration and only slightly less toxic after subcutaneous injection. Therefore, it should be injected with caution. For corneal anesthesia larocaine is used in two to five per cent concentrations. In the nose and throat, five to 10 per cent solutions are employed. A one per cent solution is used in urological work. For injection anesthesia, strengths varying from one-quarter to two per cent are recommended. The available salt is the hydrochloride.

Metycaine

Metycaine, N.N.R., is an ester of benzoic acid and a base containing nitrogen in the form of a methyl-piperidino ring. It has the following structural formula:

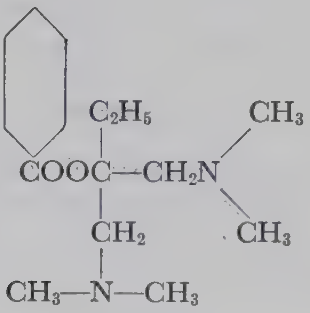


Metycaine

Metycaine is suitable for topical anesthesia and for the production of nerve block. It is about three times as toxic as procaine upon intravenous injection, but approaches the toxicity of procaine after subcutaneous administration. Metycaine is used in the eye as a two per cent solution or a four per cent ophthalmic ointment. In the nose and throat, two to 10 per cent solutions are applied. For anesthetizing the mucous membranes of the genitourinary tract, concentrations ranging from one to four per cent have been employed. For injection anesthesia, one-half to one per cent solutions are used. Metycaine is obtainable as the hydrochloride salt.

Alypin

Alypin, N.N.R., is also a tertiary amino ester of benzoic acid and has the following structural formula:

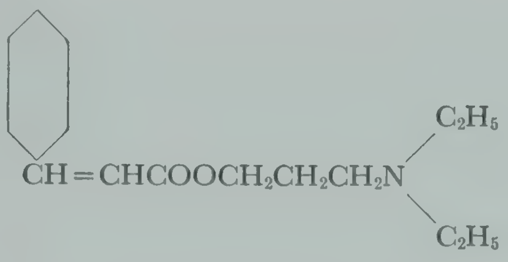


Alypin

Alypin is quite as toxic as cocaine and its use should therefore be limited to surface application to mucous membranes. When applied to the eye it does not have the disadvantages of cocaine. For ophthalmological purposes it is used in a concentration of two to four per cent. In rhinolaryngology, five to 10 per cent solutions may be employed. Alypin has also been used in urology in concentrations of one to four per cent. Although alypin has been employed for injection anesthesia in concentrations of one-half to two per cent, it is probably too toxic to be used in this manner. Alypin is available as the soluble hydrochloride salt.

Apothesine

Apothesine, N.N.R., is the diethylaminopropyl ester of cinnamic acid and has the following structure:

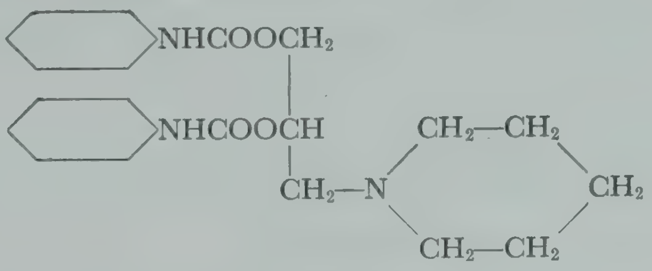


Apothesine

There is little to be said in favor of apothesine. It resembles procaine in that it is not suitable for surface application to mucous membranes, and therefore it can be used only for injection anesthesia. It is twice as toxic as procaine and no more active. Apothesine is also slower in action than procaine and is apt to produce greater irritation. Its duration of action, however, is longer. For injection anesthesia, apothesine is used in concentrations ranging from 0.5 to 2.0 per cent. The available soluble salt is the hydrochloride.

Diothane

Diothane, N.N.R., is a phenylurethane derivative, and it can be noticed in the following structural formula that the nitrogen of the ester grouping is contained in a piperidino ring, a grouping also present in metycaine.

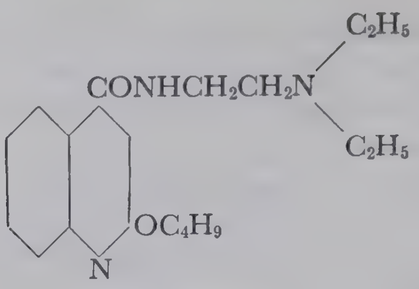


Diothane

The toxicity of diothane is less than that of cocaine and greater than that of procaine. It is active both as an injection anesthetic and after topical administration to mucous membranes. An unusual feature is the long duration of its action. Thus diothane has been used in such operations as hemorrhoidectomy or amputation of limbs. It is usually employed in a one per cent solution. Because of its fairly high toxicity, the total amount injected should be kept as low as possible. Diothane is available in solution as the hydrochloride salt and as a one per cent ointment.

Nupercaine

Nupercaine, N.N.R., is a quinoline derivative of high toxicity and high anesthetic potency. It has the following structure:



Nupercaine

It is about six times as toxic as cocaine upon intravenous injection, and twelve times as toxic as cocaine after subcutaneous administration. However, the high anesthetic potency of nupercaine suggests that it may have a greater margin of safety than cocaine (Table 15). Nupercaine has been used for all types of local anesthetic procedures. It is the most potent and most toxic of the commonly employed local anesthetics, and several deaths have been reported from its use. Although tissue damage has followed the employment of nupercaine, there is no reason to believe that it is more injurious to tissue than are other local anesthetics.

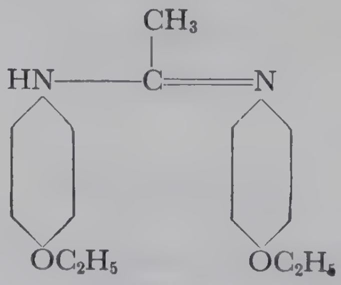
There is evidence that nupercaine is rapidly destroyed by the liver. It also provides anesthesia of long duration. Some surgeons recommend that advantage be taken of these two features by administering a preliminary anesthetizing dose of nupercaine thirty minutes before operation. At the time of operation, this preliminary anesthetic dose will still be effective with respect to anesthesia, and yet the material absorbed will have been destroyed. This permits further administration of nupercaine which results in still more effective anesthesia.

Nupercaine is employed for injection anesthesia in 0.05 to 0.1 per cent solution (1:2000 to 1:1000). Its combination with epinephrine is important inasmuch as low concentrations are likely to cause some capillary dilatation. When used in 0.1 per cent concentration, the total amount of nupercaine solution injected should not exceed 100 cc. Some anesthetists consider this amount too high. Death has been reported from the administration of 135 cc of a 1:1000 solution. For surface anesthesia, nupercaine may be employed as follows: cornea, 0.1 per cent solution; nose and throat, 0.5 to 2.0 per cent solution; urethra, 0.05 to 0.2 per cent solution; skin, 0.5 to 1.0 per cent ointment. Nupercaine is marketed as the soluble hydrochloride salt.

In view of its high toxicity, nupercaine should be used only by those thoroughly familiar with the drug and with the technic of local anesthesia.

Phenacaine

Phenacaine was one of the earliest local anesthetics to be introduced and is official in the U.S.P. as the hydrochloride salt. It differs greatly in chemical structure from the majority of local anesthetics thus far described. Phenacaine is a derivative of phenetidin and was built up from this structure because of the known antineuralgic effects of the phenetidin molecule. Phenacaine is not an ester, as can be seen from its structural formula:



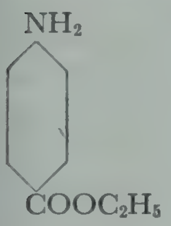
Phenacaine

Upon intravenous injection phenacaine is as toxic as cocaine. It is not as readily destroyed as cocaine in the body, as is indicated by the fact that its subcutaneous toxicity is twice as great as that of cocaine. For this reason, it is unsuitable for injection and its use is limited to topical application, especially to the eye. A one per cent solution is employed. Phenacaine is slightly irritating and anesthesia is preceded by smarting. *Holocaine* (N.N.R.) is a brand of phenacaine.

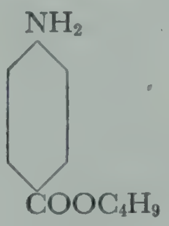
Anesthetics of Low Solubility

This group of local anesthetics is characterized by the fact that its members are poorly soluble in water. Obviously, this seriously limits their usefulness, but it opens special fields of application. As a result of their insolubility, these compounds can be applied directly to wounds and ulcerated surfaces because they are not absorbed with sufficient rapidity to be toxic. Thus they remain localized at the site of application for long periods of time, which accounts for their sustained anesthetic action.

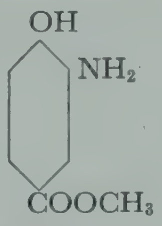
Chemically, the poorly soluble local anesthetics are closely related to the procaine group in that they are esters of aminobenzoic acid. They differ in being simple esters and contain no basic nitrogen grouping. Consequently they do not form soluble acid salts. The most important members of the series are *Ethyl Aminobenzoate* (Benzocaine), U.S.P., B.P., also known as Anesthesin; *Butesin*, N.N.R.; *Butesin Picrate*, N.N.R.; *Orthoform*, N.N.R. (Orthocaine, B.P.). All are white, crystalline, insoluble powders with the exception of butesin picrate which is yellow and amorphous. They have the following structural formulas:



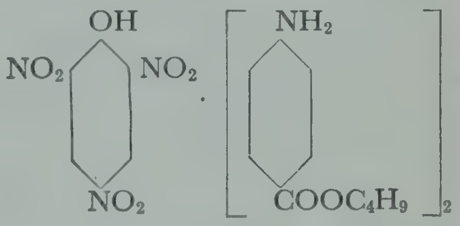
Ethyl Aminobenzoate



Butesin



Orthoform

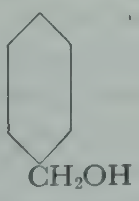


Butesin Picrate

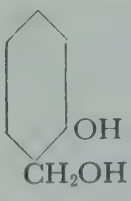
The aforementioned compounds may be applied as dusting powders, undiluted or diluted with sterile talc. They are soluble in oil and may be incorporated in oily solutions, ointments, and suppositories. Specific indications for these drugs are described under the clinical uses of the local anesthetics. Butesin picrate is unique in that it incorporates the anesthetizing properties of butesin with the antiseptic properties of picric acid.

Aromatic Alcohols

Certain aromatic alcohols have the property of producing local anesthesia. The two most important are *Benzyl Alcohol*, N.N.R., a colorless liquid, and *saligenin* (salicylic alcohol), a colorless crystalline solid soluble in water to the extent of 1:15. These compounds have the following structural formulas:



Benzyl Alcohol



Saligenin

The anesthetic potency of benzyl alcohol was studied by Macht (1918). In favor of benzyl alcohol is the fact that it is relatively non-toxic, being converted to hippuric acid in the body. On the other hand, the anesthesia following its use is uncertain, and accompanying its injection there may be subcutaneous edema and pain. Benzyl alcohol is soluble in water to the extent of four per cent, and in this concentration it has a brief anesthetic action after topical application to mucous membranes. One to four per cent solutions may be used for injection anesthesia. Benzyl alcohol has been employed in the form of an ointment or lotion to control cutaneous itching. This constitutes its most legitimate use. A simple antipruritic lotion can be made by combining equal parts of benzyl alcohol, ethyl alcohol and water.

Saligenin is also relatively non-toxic. Two per cent solutions may be used for injection anesthesia and four to eight per cent solutions anesthetize the urethra sufficiently for purposes of cystoscopy. The relationship between saligenin and the salicylates is discussed elsewhere.

Quinine Salts

Certain salts of quinine are sometimes employed as local anesthetics. *Quinine and Urea Hydrochloride,* U.S.P. is the preparation of choice because it is the most soluble and least irritating. However, it is acid in solution and irritates before it produces anesthesia. The anesthetic action of quinine and its derivatives is directly proportional to its toxicity for protoplasm. There is reason to believe, therefore, that the action of quinine on sensory nerves is non-selective and is merely the result of the toxic action of the alkaloid on protoplasm. The anesthetic action of quinine is of long duration and several weeks may elapse before nerve function is completely restored. In contrast to other local anesthetics, quinine has a pronounced effect on the tissues at the site of injection, and edema and exudation accompany its use. Often there is an area of hyperesthesia surrounding the area of anesthesia. Quinine may be of particular value in conditions where anesthesia of long duration is desired as in pruritus ani. If the concentration of the solution employed is greater than 0.5 to 1.0 per cent, extensive necrosis may follow. In ointment form, quinine has been employed to anesthetize painful hemorrhoids. An advantage of quinine salts as local anesthetics is their relatively low systemic toxicity. The pharmacology and therapeutics of quinine and its salts are described elsewhere.

CLINICAL USES OF LOCAL ANESTHETICS

The following discussion can do no more than indicate the fields of usefulness of the local anesthetics, the criteria for their selection, the precautions to be observed in their employment, and the general principles of technic. Special texts must be consulted for the practical details of local anesthetic procedures.

It should always be remembered that the local anesthetics are toxic drugs, and certain precautions should be observed to lessen their toxicity.

Preliminary Sedation. Most local anesthetics are central nervous system stimulants, and they are likely to produce convulsions, especially if they are employed in large amounts. In sensitive individuals, convulsions may follow the administration of relatively small doses. Although it is possible by means of central depressants to control such reactions after they have become manifest, a far safer procedure is routinely to precede the administration of a local anesthetic with a sedative. The barbiturates are the preparations of choice. The barbiturate selected should have a duration of action sufficiently long to insure that the complete absorption and destruction of the local anesthetic have occurred before the effects of the sedative have worn off. Barbital is often administered in a dose of 0.5 to 0.67 gram one hour before the local anesthetic is given. Phenobarbital in a dose of 0.15 to 0.2 gram is also serviceable.

Choice of Anesthetic. When a local anesthetic is to be injected, the least toxic one should be employed. Procaine is considered the safest agent available for this purpose. Procaine should be employed in the lowest concentration and the smallest total amount compatible with the needs of the surgical procedure. For anesthetizing mucous membranes, agents of greater penetrative power than procaine are necessary. Cocaine is widely used as a surface anesthetic but several synthetic substitutes are available and on occasion preferable. No single compound is outstanding for surface anesthesia. The clinician would be wise to limit his choice to one or two Council-accepted agents that have stood the test of clinical trial. In this way he can become thoroughly familiar with their effective concentrations, limitations and toxicity. A working knowledge of one good surface anesthetic and procaine is sufficient for practically all local anesthetic procedures. The clinical trial of new local anesthetic agents should be restricted to experts in this field.

Due to the high incidence of accidents from the use of local anesthetics, the American Medical Association appointed a special committee to investigate the problem. This committee (Mayer, 1924) made several recommendations of which the following are the more important: (1) Cocaine and butyn should be restricted to surface application; (2) the total amount of cocaine used should not exceed 0.1 gram; (3) procaine may be employed as an injection anesthetic, but its concentration should be limited to 1.0 per cent; (4) anesthetic agents should not be injected into the urethra if there is trauma, inflammation or stricture (*see* Report of the Council, 1939); (5) precautions should be taken not to confuse cocaine and procaine, inasmuch as a number of fatalities have occurred from this error.

Technics for Local Anesthesia

Surface Anesthesia. The aqueous solutions of salts of local anesthetics do not penetrate the intact epidermis. Preparations of the anesthetic bases in ointments, however, accomplish this to a limited extent. For application to wounds and ulcers for the relief of pain, the insoluble compounds already described are the preparations of choice. They are relatively safe and, if properly used, do not interfere with tissue healing. After prolonged administration there is some evidence that they may produce tissue damage and delay healing. Their ingestion for the relief of gastric pain or vomiting has little rational basis. A more legitimate use is found in the relief they afford after tooth extraction, tonsillectomies, etc. They are frequently incorporated in troches for the symptomatic relief of sore throat.

Anesthesia of the mucous membranes of the nose and throat can be produced by painting or spraying solutions of any of the agents which penetrate these membranes. The concentrations employed have already been given for the individual anesthetics. The mucous membranes of the urogenital tract are often anesthetized prior to instrumentation or surgical procedures. The intra-urethral injection of local anesthetics has led to many accidents, and the precautions cited should be rigidly observed. The cornea of the eye is easily anesthetized by topical application of solutions of local anesthetics. The more potent agents can be employed with safety for there is little absorption from this site. The advantages of butyn over cocaine for corneal anesthesia have already been described Anesthetic agents may also be applied to the eye and mucous membranes in the form of ointments.

Infiltration Anesthesia. This technic has for its purpose the anesthetizing of nerve endings by their direct exposure to the drug. The solution may be injected into the papillary layer of the skin (endermic injection). The onset of cutaneous anesthesia is almost immediate and very little of the anesthetic need be employed. Subcutaneous injection of the drug carries the anesthesia to a deeper level but allows for greater absorption. In addition, a short interval is required before the onset of anesthesia. After the skin is anesthetized, the deeper structures may be infiltrated if necessitated by the surgical procedure. A type of infiltration commonly employed is known as *ring block.* In this procedure the anesthetic is not injected at the site of operation, but instead is infiltrated subcutaneously in a circular manner around the line of incision. This effectively blocks all sensory nerves supplying the skin over the operative field.

Block Anesthesia. The technics of block anesthesia have greatly increased the usefulness of local anesthetics. In block anesthesia the transmission of impulses in the nerve trunks supplying the operative area is interrupted. Obviously the extent of the anesthesia produced depends upon the distribution of the nerves which are blocked. In the case of a peripheral nerve, only a discrete area is anesthetized. On the other hand, the transmission of nerve impulses in the spinal cord itself may be blocked. The extent of the anesthesia depends upon the segments of the spinal cord which are involved. In the production of nerve block, two or three cc of a one per cent solution of procaine (or an equipotent concentration of any other drug of choice) are injected in the immediate vicinity of the nerve trunks which supply the area of operation. In many of these block procedures, experience is necessary to insure success and more and more the responsibility for administration of local anesthetics is being delegated to specialists in this field.

Paravertebral Block. This is an extensive form of block anesthesia in which the spinal nerves are blocked at their point of exit from the intervertebral foramina. It is usually employed only by specialists in anesthesia. It may be of particular value in certain cases of thoracic surgery. For operations in the lower abdomen, however, spinal anesthesia is simpler and probably safer.

Trans-sacral block is used for anesthetizing the bladder, prostate, rectum and perineum. The anesthetic is injected around the sacral nerves at their points of exit from the sacral foramina. Multiple injections and a high degree of skill are required to block all branches of these nerves. An alternate method of producing sacral block is to pass a needle through the sacral hiatus and inject the anesthetic solution into the epidural space.

Spinal Anesthesia. Spinal anesthesia is a special type of extensive block anesthesia. The first spinal anesthesia in man was performed by Bier in 1899. For a short time thereafter, this type of anesthesia enjoyed popularity. A high incidence of deaths, however, brought it into disrepute. Two factors especially contributed to the dangers attending the early use of spinal anesthesia. The anesthetic agent then employed, cocaine, was too toxic to be administered in this manner. Also, the physiological effects of a local anesthetic in the spinal canal were not appreciated and consequently no precautions were taken to circumvent the attending dangers.

Action of Local Anesthetics in the Spinal Canal. The action of local anesthetics in the spinal canal is to block nerve conduction. If it were possible to confine the action to a desired locus, the performance of spinal anesthesia would be simple. In actual practice, many factors operate to complicate the procedure. The local anesthetics tend to spread along the length of the spinal canal. All types of nerve fibers—sensory, motor, somatic and autonomic—are functionally blocked and this may result in a severe if not fatal incapacitation of the vital processes.

Sequence and Duration of Anesthesia. Following the intrathecal injection of a local anesthetic there is a definite sequence in which the various types of nerve structure are paralyzed. In human beings, the sensory nerves are the first to be affected. Sensory block occurs within two to eight minutes (average four). Autonomic fibers are blocked about one minute later. This is manifested by a rise in skin temperature due to the involvement of the vasoconstrictor fibers of the anterior nerve roots. Within a few minutes thereafter motor paralysis appears. As the anesthesia wears off, function is regained in the opposite order, motor activity being the first to be restored. The duration of spinal anesthesia is often shorter than is desirable. For example, procaine anesthesia lasts for only one hour following the administration of concentrations compatible with safety. Other drugs act for longer periods, nupercaine having the greatest duration (three hours). Duration of anesthesia can be lengthened by increasing the concentration of the anesthetic solution.

Level of Anesthesia. Local anesthetics are usually injected into the subarachnoid space between the conus medullaris and the terminal portion of the spinal canal, in order to avoid injury to the spinal cord. In the adult, therefore, the injection is ordinarily made through one of the vertebral interspaces between the first and fourth lumbar levels. Obviously upward diffusion of the anesthetic agent must take place in order for extensive sensory paralysis to result, and the topography of the anesthetic area depends upon the extent of this diffusion. The skillful anesthetist limits the area of anesthesia to the minimum necessary for the contemplated surgical procedure. The upward passage of an anesthetic agent in the spinal canal depends upon a multitude of factors, among them being the diffusion currents within the subarachnoid space, the specific gravity of the injected solution, the plane of the spinal canal relative to the horizontal, movements of the patient, etc. The following are the more important procedures utilized to control the level of anesthesia.

Site of Injection. Inasmuch as the sites of injection are limited, this is a relatively unimportant factor. Some anesthetists inject at the same level and utilize other variants to control the level of anesthesia. Others vary the site of injection from the extremes of L_5 for operations on the perineum to D_{12} for upper abdominal operations.

Volume of Solution. Local anesthetics are usually dissolved in spinal fluid, previously withdrawn for this purpose. The volume of the anesthetic solution which is injected greatly influences the level of anesthesia obtained. The area of anesthesia becomes more extensive as the volume of anesthetic solution is increased. The volume injected is varied in clinical practice between one and 10 cc or more, depending upon the level of anesthesia desired and the extent to which this variable is being utilized to control the anesthesia.

Total Amount of Anesthetic Agent. The total amount of anesthetic agent used must be sufficient to provide a concentration of the drug in the spinal fluid capable of producing nerve block and also to permit an adequate duration of anesthesia. The greater the amount of anesthetic agent injected, the greater is the area anesthetized and the longer the duration of anesthesia. Low abdominal operations require a relatively small amount of drug for little upward diffusion is necessary and the anesthetic agent does not become diluted with a large volume of spinal fluid. As the extent of the area to be anesthetized is increased, the total dose must be raised. The degree to which the total dose is varied depends upon how much this particular factor is being used to control the level of anesthesia. Obviously the relative doses of the individual anesthetic agents vary with their potency.

Speed of Injection. Solutes diffuse slowly in the spinal fluid unless currents are set up to speed the process. For example, the force of injection of the anesthetic agent may be an important factor in determining the extent of diffusion. The more rapid the rate of intrathecal injection, the higher is the level of anesthesia obtained. In practice, however, a slow rate of injection is utilized because the level of anesthesia cannot be accurately regulated by varying this factor.

Position of Patient. Anesthetic solutions dissolved in spinal fluid naturally have a specific gravity higher than that of the spinal fluid. Therefore the rate of diffusion can be influenced by the position of the patient. The level of anesthesia can be raised by placing the patient in the Trendelenburg position immediately after injection. A horizontal position minimizes upward diffusion. Some anesthetists vary the specific gravity of the anesthetic solution by the addition of such a substance as glucose.

TABLE 16

REPRESENTATIVE TECHNICS FOR SPINAL ANESTHESIA OF FIVE DIFFERENT ANESTHETISTS *

	PERINEUM	LOWER ABDOMEN	MID-ABDOMEN	UPPER ABDOMEN
PROCAINE				
Dose in mgm	100	120	120	150
Dilution in cc	3	5	5	5
Trendelenburg	+	+	+	+
Site of puncture	L_3	L_2	L_1	D_{12}
PROCAINE				
Dose in mgm	60	100	120	120
Dilution in cc	3	5–9	7–9	8–11
Trendelenburg	0	0	0	0
Site of puncture	L_5	L_3	L_3	L_2
PROCAINE				
Dose in mgm	100	150	150	200
Dilution in cc	1	1.5	2	2.5
Trendelenburg	0	0	0	0
Site of puncture	$L_2 - L_3$	$L_2 - L_3$	$L_2 - L_3$	$L_2 - L_3$
NUPERCAINE				
Dose in mgm	10	10	10	10
Dilution in cc	2	5	8	10
Trendelenburg	+	+	+	+
Site of puncture	L_3	L_3	L_3	L_3
METYCAINE				
Dose in mgm	40–80	120	140	180
Dilution in cc	2	4–5	5	5
Trendelenburg	0	+	+	+
Site of puncture	L_4	L_3	L_3	L_3

* From data presented by Saklad (1936).

Table 16, compiled from data presented by Saklad (1936), illustrates different technics for the administration of spinal anesthesia and the utilization of the various factors outlined for the control of the level of anesthesia.

Toxic Effects of Spinal Anesthesia. Respiration. A local anesthetic in the spinal canal can depress respiration in two ways. As the drug diffuses upward into the thoracic area, the motor nerves to the muscles of respiration are paralyzed. The intercostal nerves are successively blocked and respiration becomes progressively more shallow and diaphragmatic in nature. When the roots of the phrenic nerves are reached, diaphragmatic breathing stops. If an anesthetic is injected in the cervical region of the cord and allowed to diffuse downward, the movements of the diaphragm cease earlier than those of the intercostal muscles. If an anesthetic drug is injected into the cisterna magna or the fourth ventricle all types of respiratory movements cease simultaneously after a very short interval, signifying that medullary paralysis has been the cause of the respiratory failure (Hill and Macdonald, 1935) (Figure 25). There is a controversy in regard to this last point, some investigators presenting experimental evidence suggesting that local anesthetics may be applied directly to the medulla without causing paralysis of vital centers. Without pursuing this question further, it may be stated that exception has been taken to the technic and interpretation of those experiments which minimize the vulnerability of the medulla to the action of local anesthetics. It is difficult to see why the medulla should respond differently to local anesthetics than do other portions of the cerebrospinal axis.

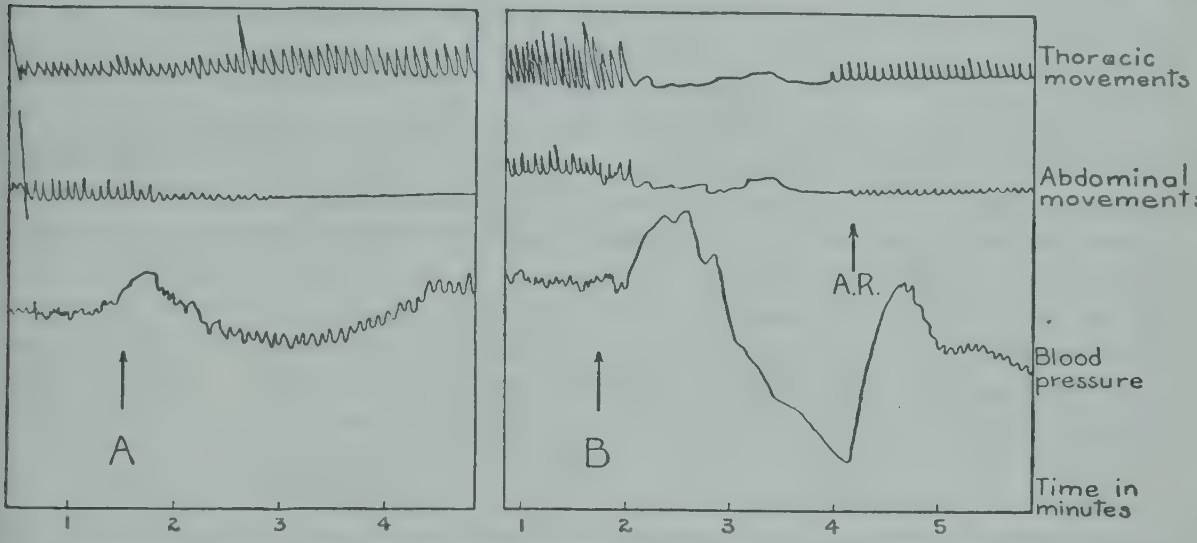


FIGURE 25. *The effects on respiratory movements of procaine injected into the subarachnoid space of chloralosed cats.*

At *A*, 10 mgm of procaine benzoate in 0.1 cc of solution are injected intrathecally at the level of C_3. The anesthetic blocks the roots of the phrenic nerves, and abdominal respiration ceases in less than two minutes due to paralysis of the diaphragm. There is a compensatory increase in thoracic respiration and the blood pressure is thereby sustained. At *B*, the same dose of procaine is injected into the cisterna magna and gains direct access to the respiratory center. All respiratory movements are immediately slowed and then simultaneously and rapidly paralyzed. The transient rise in blood pressure is due to anoxia secondary to apnea, and the subsequent marked fall in pressure is checked by the administration of artificial respiration (A.R.). (After Hill and Macdonald, 1935. Courtesy of the *Journal of Pharmacology and Experimental Therapeutics.*)

The susceptibility of the respiratory nerves and centers to the action of local anesthetics is one of the greatest handicaps to the extensive clinical employment of spinal anesthesia. In order to attain anesthesia adequate for upper abdominal surgery, the spinal block must extend to the level of T_5. In practice it often rises above this level and respiration may be seriously embarrassed. Obviously spinal anesthesia cannot be safely employed for surgery above the level of the abdomen.

During the first half-hour of spinal anesthesia the anesthetist is constantly on the alert to ascertain how high motor paralysis has extended. Signs of impending respiratory paralysis are the diminution of thoracic respiration with increasing diaphragmatic excursions, loss of spoken voice, dilatation of the alae nasi, and the use of the accessory muscles of respiration with dropping of the jaw with each respiration (Saklad, 1936). A failing respiration during spinal anesthesia calls for physical measures rather than drug therapy inasmuch as the failure is on the motor side and cannot be influenced by respiratory stimulants. If some muscle function remains, the administration of pure oxygen may be sufficient to keep the blood adequately oxygenated. Complete muscular paralysis necessitates artificial respiration. An intratracheal tube should be passed to assure an open airway.

Circulation. Following the intrathecal injection of a local anesthetic in a concentration adequate to produce nerve block, there is a progressive fall in systemic blood pressure. This is due mainly to a loss of vasomotor tone which follows the paralysis of the vasoconstrictor fibers in the anterior nerve roots. Other factors which may contribute are the loss of skeletal muscular tone in the anesthetized areas and a certain degree of anoxia due to respiratory depression. The fall in blood pressure is progressive for the reason that reflex control of blood pressure is inoperative due to the extensive paralysis of the sympathetic vasomotor outflow. For example, Heymans and coworkers (1933) have shown that when a local anesthetic rises sufficiently high in the spinal canal to produce sensory paralysis at the level of the umbilicus, the blood pressure may not be seriously depressed but carotid sinus reflexes no longer operate effectively. When sensory anesthesia reaches the level of the clavicle, there is a profound and prolonged fall in blood pressure and the carotid sinus reflexes are completely lost.

Despite the fact that the cardiac nerves are not paralyzed at levels of spinal anesthesia which cause a significant fall in blood pressure, the heart rate is not reflexly speeded. The beat, however, is forceful and the pulse pressure is high. Some investigators have attributed this to a vagal stimulation but the cause is not clear. Seevers and Waters (1932) have shown that during spinal anesthesia in dogs there is a rise in venous pressure. This promotes good filling of the right heart, forceful ventricular contractions, and adequate cardiac output, factors which may account for the relatively slow cardiac rate.

The lack of compensatory circulatory reflexes under spinal anesthesia renders the patient especially susceptible to hemorrhage inasmuch as the volume capacity of the circulatory system cannot be reduced to meet a diminished blood volume. Under such circumstances, venous pressure falls and tachycardia results. This is a dangerous sign during spinal anesthesia. Immediate measures to maintain blood volume should be taken (page 587).

The fall in blood pressure during spinal anesthesia would at times be an insurmountable obstacle to the clinical use of this type of block were it not for the fact that it can be successfully combated by the use of drugs. A sympathomimetic stimulant of long duration of action is indicated and the drug which best answers the purpose is ephedrine. Ephedrine is routinely administered by most anesthetists prior to the induction of spinal anesthesia. The doses employed vary between 50 and 100 mgm. The drug compensates sufficiently for the extensive sympathetic vasomotor block to prevent any significant fall in blood pressure. Ephedrine medication may be eliminated when the action of the local anesthetic is confined to the lower portions of the cord.

The foregoing views on the mechanism of the circulatory changes during spinal anesthesia are those which are accepted by the majority of investigators. In a significant paper, however, Smith, Rovenstine, Goldring, Chasis and Ranges (1939) seriously question the validity of these concepts, and present evidence in favor of the interpretation that circulatory failure during spinal anesthesia is the result of a pooling of blood in the venous side of the circulatory tree subsequent to the loss of tone of skeletal muscle.

Smith and coworkers experimented on normal, unoperated human subjects under spinal anesthesia. That the sympathetic fibers in the anterior nerve roots were completely paralyzed was demonstrated by the fact that the subjects showed no reflex circulatory response to such procedures as postural changes and the inhalation of carbon dioxide. The authors then showed that, despite the sympathetic block, their subjects gave little evidence of arteriolar dilatation. They present the following arguments: (1) Although there was a fall of blood pressure during spinal anesthesia, the pressure responses observed from the point of view of hemodynamics were not consonant with arteriolar dilatation, in that the diastolic pressure was well maintained while the systolic and pulse pressures were reduced. The authors point out that moderate arteriolar dilatation would be revealed by a substantial increase in pulse pressure at the expense of the diastolic pressure. (2) The changes in blood pressure observed could be explained on the basis of what would be expected when the peripheral resistance remains relatively unchanged while the cardiac output is reduced. Smith and coworkers believe that in their studies a decreased venous pressure accounted for a reduced stroke volume and cardiac output. Although they made no measurements of cardiac output, they cite from the literature many instances in which spinal anesthesia was shown experimentally to be associated with a reduced cardiac output. The decrease in venous return was attributed by Smith and coworkers to the loss in tone of skeletal muscle resulting in a dilatation of capillaries, venules and veins. In one of their patients, tilting at an angle of 20 degrees from the horizontal resulted in circulatory collapse (Figure 26). The parallelism between this response and nitrite syncope (Figure 60) is obvious. The mechanism of nitrite syncope is also believed to be due to a pooling of blood in the venous system (page 556). (3) Careful measurements of the blood flow through the kidney failed to reveal significant changes in renal circulation incident to blocking the efferent sympathetic pathways to the organ by spinal anesthesia.

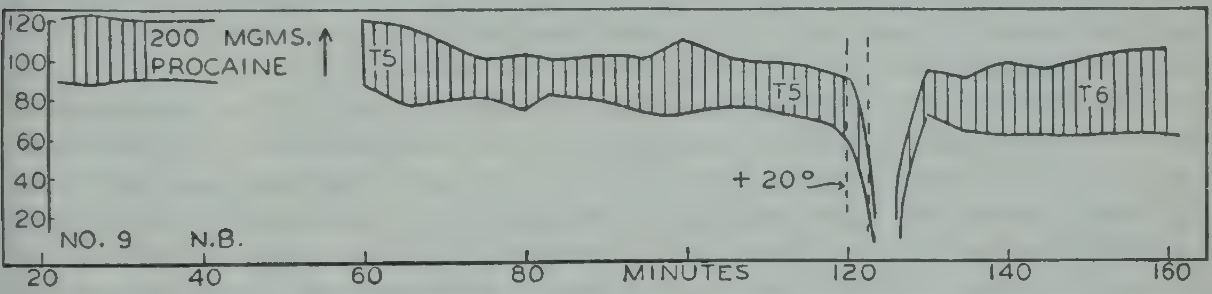


FIGURE 26. *The effect of spinal anesthesia and subsequent postural changes on blood pressure.*

Normal subject under spinal anesthesia (procaine). The effect of the anesthetic in the spinal subarachnoid space while the subject was in the horizontal position was to decrease the mean blood pressure from 106 to 90 mm of mercury. Tilting toward the upright position resulted in syncope, which may be attributable to venous stagnation aggravated by gravity. Note the similarity to nitrite syncope (Figure 60). (After Smith, Rovenstine, Goldring, Chasis and Ranges, 1939. Courtesy of the *Journal of Clinical Investigation.*)

Smith and coworkers agree that spinal anesthesia blocks sympathetic efferent fibers. They take exception, however, to the physiological significance which other investigators place upon such a block. It is their claim that after autonomic denervation the arterioles of the splanchnic viscera and probably skeletal muscles possess sufficient autonomy to maintain a normal blood pressure. They make this claim on the basis of their own observations on the renal circulation, and from an exhaustive summary of the literature on this subject.

It is difficult on the basis of the interpretation of Smith and associates to explain the salutary effects of ephedrine during spinal anesthesia. Also one would expect an increased heart rate during spinal anesthesia attending a fall in systolic blood pressure occasioned by a decrease in venous return and cardiac output. On the other hand, there is little doubt that, attending arteriolar dilatation, decreased peripheral resistance, and adequate venous return, an increase in pulse pressure should readily be noted. Accurate measurements of venous pressure and cardiac output on a large number of patients under spinal anesthesia must be awaited before a final conclusion can be reached.

Nerve Injury. Rarely spinal anesthesia is followed by radiculitis and myelitis. These infrequent toxic sequelae are attributed by some investigators to faulty technic but others believe that they arise from a direct toxic action of local anesthetics on nerve tissue. This subject has been extensively reviewed by Light and coworkers (1940).

Systemic Toxicity. Absorption of local anesthetics from the spinal canal does not readily occur. Nevertheless, intrathecal injection of anesthetic agents occasionally may give rise to characteristic systemic poisoning. Inasmuch as the amounts of drug injected for spinal anesthesia are much lower than those used for the usual types of infiltration or block anesthesia it must be assumed that such responses occur mainly in hypersensitive individuals.

Advantages of and Indications for Spinal Anesthesia. Spinal anesthesia may have definite advantages over general anesthesia. It gives an extreme degree of muscular relaxation which is obtainable only under the deepest planes of general anesthesia. The patient does not lose consciousness. In some individuals this fact removes a source of apprehension. Patients with cardiac disease may tolerate spinal anesthesia better than general anesthesia. In the presence of pulmonary disease such as bronchitis, bronchiectasis, emphysema, active tuberculosis and asthma, spinal anesthesia is often to be preferred. Diabetes and renal disease also may be indications for its use, because this type of anesthesia has little effect on blood sugar and does not irritate the kidneys.

Disadvantages of and Contraindications to Spinal Anesthesia. The untoward effects of spinal anesthesia on the respiration and circulation are its chief disadvantages. The conservative surgeon, therefore, limits the use of spinal anesthesia to operations on the lower abdomen, pelvis and lower extremities. Nausea and vomiting frequently accompany spinal anesthesia but the reason for this is unknown. It is usually precipitated by a sudden movement of the patient or traction on viscera. Motor activity of the gastro-intestinal tract may be greatly enhanced by spinal anesthesia, due to the block of the thoracolumbar sympathetic inhibitory innervation of the bowel (Burstein, 1939). This sometimes is a great inconvenience or even a danger and may contraindicate the use of spinal anesthesia in patients with intestinal obstruction or peritonitis. Atropine and ephedrine may be employed to overcome the enhanced gastro-intestinal activity. Postanesthetic headache is common following spinal anesthesia. It probably results from the loss of spinal fluid through the needle wound of the dura rather than from a direct action of the anesthetic agent.

Patients suffering from hemorrhage or shock respond poorly to spinal anesthesia for reasons mentioned. This type of anesthesia should not be used for patients with hypertension or hypotension. Cerebrospinal disease and the presence of skin infection at the site of injection constitute additional contraindications.

The strongest argument against the routine use of spinal anesthesia is the statistical evidence that general anesthesia is a safer procedure. The incidence of death due to spinal anesthesia is placed at approximately one fatality in 3000 cases, a much higher ratio than for general anesthesia. In accounting for the mortality figures, however, it should be pointed out that the type of patient who receives a spinal anesthetic is often a poor surgical risk.

Preanesthetic Medication. Preanesthetic medication for spinal anesthesia is much the same as for general anesthesia. It is mainly for the purpose of calming the patient, dulling his senses and removing apprehension. The usual routine is to administer a barbiturate the night before and morphine and scopolamine one hour before operation. A short-acting barbiturate may also be given before operation but this is not mandatory as is the case prior to other types of injection anesthesia. Systemic reactions characterized by stimulation of the central nervous system are rare following the intrathecal injection of local anesthetics. Medullary paralysis resulting from the direct access of the anesthetic agent to the region of the medulla is more to be feared. It has been shown by CoTui (1933) that barbiturates increase the susceptibility of the medulla to paralysis by *direct* application of local anesthetics. Small doses of morphine and scopolamine do not have this effect.

Supplementary Anesthesia. Spinal anesthesia is of relatively short duration and if a surgical procedure lasts longer than is anticipated, it may be necessary to administer supplemental anesthesia. Often infiltration anesthesia answers the purpose but on occasions it may be necessary to superimpose general anesthesia. In such an instance, an anesthetic agent which can be given with large amounts of oxygen should be employed, for the tissues of the patient under spinal anesthesia are likely to be slightly anoxic, especially if there is respiratory depression or hypotension. The best general anesthetic to employ is cyclopropane. The intravenous injection of barbiturates should be undertaken with care because of the possible deleterious effects on the blood pressure and respiration.

Choice of Anesthetic Agent. The local anesthetics most commonly employed for spinal anesthesia are procaine, metycaine and nupercaine. Procaine is the safest, least irritating, and by far the most widely used. Its chief disadvantage is its short duration of action, anesthesia lasting about one hour. Some anesthetists use combinations of these agents in order to increase the duration of anesthesia.

Epidural Anesthesia. Epidural anesthesia is an extensive form of block anesthesia produced by injecting a local anesthetic into the epidural space. With this technic sensory anesthesia extending as high as the chin can be produced without seriously affecting respiration or circulation.

Technic. At the foramen magnum the cranial dura splits into two layers. The inner layer becomes the dura of the spinal cord. The external layer forms the periosteal lining of the spinal canal. Between these two layers is the epidural space which contains semiliquid fat and venous plexuses. The epidural space varies in extent, being largest at the level of the second lumbar vertebra where it occupies approximately one-half the diameter of the spinal canal. The spinal nerves traverse this space after the anterior and posterior nerve roots have joined within the subarachnoid space and obtained their dural sheath.

In carrying out an epidural anesthesia, the usual procedure is to enter the space at the level of L_2. The entrance of the needle can be conveniently detected inasmuch as a negative pressure exists in the epidural space and fluid (in a suitable glass indicator) can be seen to be aspirated. The anesthetic solution is then slowly administered.

Several technics of epidural anesthesia have been devised. The following is that of Odom (1936). From 35 to 50 cc of two per cent procaine are necessary for adequate anesthesia. The extent of epidural anesthesia is governed by the volume of fluid injected and the position of the patient. Employing the Trendelenburg position following the injection of 50 cc, anesthesia extends upward to the level of the chin. After smaller volumes and using the Fowler position, however, anesthesia can be limited to the perineal region. If the contemplated surgical procedure is on one side of the midline, the patient should lie on that side to facilitate the gravitation of the anesthetic toward the nerves supplying the area of operation.

Action of Local Anesthetics in the Epidural Space. Epidural anesthesia refers to the site of injection rather than to the site of nerve block. Within the epidural space the spinal nerves are covered with a thick layer of dura and it is not until the nerves leave the intervertebral foramina that this protection is lost. It is likely that after epidural injection the local anesthetic solution diffuses along the perineural lymphatics to leave the epidural space at the intervertebral foramina and block the spinal nerves outside of the spinal canal. Thus the end-result of epidural anesthesia is essentially an extensive paravertebral block.

The diffusion of a local anesthetic along the entire length of the spinal epidural space and out through the many intervertebral foramina is a relatively slow process and for this reason there is an appreciable latent period between the injection and the onset of anesthesia. Usually, within 10 minutes after injection a narrow zone of sensory paralysis is evident in the skin over the lower abdomen which is supplied by nerves originating at the level of injection. This area of anesthesia soon spreads to cover the whole body from the chin to the lower extremities. Surgical anesthesia is obtained in from 15 to 30 minutes. Complete motor paralysis is not observed, for apparently the concentration of anesthetic agent gaining access to the spinal nerves is not sufficient to block the larger and more resistant motor fibers. Sensory block persists for one and one-half to two hours. Despite the fact that motor block is incomplete, abdominal relaxation is adequate due to the interruption on the afferent side of the reflexes controlling muscle tone.

Advantages of Epidural Anesthesia. Epidural anesthesia possesses all the advantages of spinal anesthesia with few of its disadvantages. The anesthetic agent does not have direct access to the medulla or spinal cord, nor does it block the motor nerves of the respiratory muscles. Consequently this type of anesthesia can be used for thoracic as well as for abdominal surgery. Neither is the blood pressure affected as markedly as in spinal anesthesia. Even when sensory block extends to the neck, the blood pressure usually falls no more than 20 to 30 mm. Nausea and vomiting rarely occur during anesthesia and patients are free of postanesthetic headache and urinary retention.

Disadvantages of Epidural Anesthesia. Difficulty in technic probably constitutes the chief disadvantage of epidural anesthesia. If injection is mistakenly made into the subarachnoid space, the amount of anesthetic employed proves toxic. A sensible precaution is slowly to inject the first 10 cc of anesthetic solution and await the effect. If the injection has been made intrathecally, it is soon apparent that spinal anesthesia has been performed. The second major disadvantage is the large amount of drug which must be employed. This averages about one gram of procaine, and systemic reactions may result in sensitive individuals. Reactions may be controlled by the prophylactic administration of a barbiturate. Epinephrine may also be incorporated in the anesthetic solution in order to retard absorption. Because of the possibilities of systemic reactions, procaine is the safest agent to employ, although some anesthetists combine procaine with a local anesthetic having a longer duration of action. Still another disadvantage is the long latent period between the injection and the onset of anesthesia.

Indications. Epidural anesthesia may be employed to advantage when both general and spinal anesthesia are contraindicated. Thus it is of great value in debilitated individuals, in persons suffering from pulmonary disease, renal disease, and diabetes complicated by hypertension, etc. Epidural anesthesia can also be used for surgery in the upper abdomen and thorax.

Miscellaneous Uses of Local Anesthetics. The local anesthetics are often employed under circumstances when a surgical procedure is not the immediate objective but rather when the relief of pain and the abolition of vasomotor and other reflexes attending pain are desired. For example, procaine is of definite value in the treatment of fractures not requiring accurate reduction and immobilization as, for example, those of the lumbar transverse processes, vertebral spinous processes, head of the radius, epicondyle, etc. Ligamentous sprains, muscle contusions or sprains, acute traumatic synovitis, and acute bursitis are also benefited by procaine anesthesia. The use of procaine in the aforementioned conditions has been reviewed by Outland and Hanlon (1940).

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SECTION V

DRUGS ACTING ON AUTONOMIC EFFECTOR CELLS

CHAPTER 19

ANATOMICAL, PHYSIOLOGICAL AND GENERAL PHARMACOLOGICAL CONSIDERATIONS

A clear understanding of the anatomy and physiology of the autonomic nervous system is essential to a study of the pharmacology of the *autonomic drugs.** In a real sense, these drugs mimic the effects of nerve stimulation. One can often predict the action of autonomomimetic agents on various organs of the body if the responses manifested to nerve impulses are known.

Many changes have occurred in recent years in our knowledge of the functional organization of the autonomic nervous system and the rôle it assumes in maintaining the economy of the body. Perhaps the most important progress for the pharmacological interpretation of the actions of autonomic drugs has been made in the field of the chemical mediation of nerve impulses. This subject will be discussed in some detail because it has also added to our terminology, revised the distinctions between the parasympathetic and sympathetic nervous systems, reclassified nerve fibers, opened a new field of investigation for striomuscular drugs, and made contributions to therapeutics and to the surgery of the visceral nervous system.

Before discussing the pharmacology of the individual autonomic drugs, certain basic considerations which enable the student better to understand their actions and uses will be presented. These preliminary considerations are divided into three sections—*anatomical, physiological* and *pharmacological.*

ANATOMICAL CONSIDERATIONS

The autonomic nervous system is also called the visceral, vegetative or involuntary nervous system. It consists of nerves, ganglia and plexuses which provide innervation to the heart, blood vessels, glands, viscera and smooth muscles. It is therefore widely distributed throughout the body and controls the so-called automatic or vegetative functions.

Differences Between Autonomic and Somatic Nerves. A major difference between autonomic and somatic nerves is the structures which they innervate. The motor nerves of the involuntary system supply all structures of the body except skeletal muscle, which is innervated by somatic nerves. The most distal synaptic junctions in the autonomic reflex arc occur in ganglia which are entirely outside of the cerebrospinal axis, whereas the synapses of somatic nerves are entirely within the central nervous system. The nerves to skeletal muscles are medullated while the postganglionic vegetative nerves are nonmedullated. When the cerebrospinal nerves are interrupted, the structures they innervate are completely paralyzed, whereas smooth muscles and glands show automatic activity independent of intact innervation. There are, however, certain similarities between these two nervous systems. These will be described later.

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* The term "autonomic drugs" is sanctioned by long usage rather than by a strict interpretation of the mechanism of action of these drugs. Autonomic drugs act peripherally not on autonomic nerves but directly on muscle and gland cells. More correctly they should be called "drugs acting on autonomic effector cells" but this expression is too cumbersome.

Central Connections of the Autonomic Nervous System. There are two restrictions, incorrect from a physiological standpoint, which are placed upon the anatomical limits of the autonomic nervous system. First, the autonomic nervous system is often erroneously considered as a purely efferent system. Secondly, autonomic nerves and ganglia are too frequently viewed as being entirely peripheral in their organization.

Visceral Afferent Nerves. The afferent nerves coming from visceral structures serve to complete the reflex arcs of the autonomic system. With the exception of the axon reflex, all visceral reflexes are mediated through the central nervous system. The afferent nerves are for the most part medullated fibers and are carried into the cerebrospinal axis by the vagus, pelvic, splanchnic, and other vegetative nerves. For example, about one-half the splanchnic nerve fibers are sensory. Other autonomic afferent fibers are carried in the cerebrospinal nerves from blood vessels in muscles and from certain integumental structures. The cell bodies of these afferent fibers lie in the dorsal root ganglia of the spinal nerves and the sensory ganglia of certain cranial nerves. Their proximal processes enter the spinal cord through the dorsal spinal roots to connect directly or through internuncial neurones with cells lying in the lateral horns. These cells send axones to synapse with other neurones in the autonomic ganglia which lie outside the central nervous system. The ganglion cells are in reality anterior horn cells which have migrated from the developing neural tube. They give origin to the last neuronal link in the reflex arc and their axonal fibers end in the effector organs. A special example of an autonomic afferent system is that arising from the vasosensitive and chemoreceptive endings in the carotid sinus, carotid body and aorta. This system assists in the reflex control of blood pressure, heart rate and respiration, and its afferent fibers pass in the glossopharyngeal and vagus nerves to the medulla.

There are no striking differences between visceral and somatic afferent nerves, and their responses to drugs do not differ. The autonomic drugs do not act specifically on autonomic sensory nerve structures. The clinical importance of these nerves arises especially in connection with the surgical relief of visceral pain. For example, it has been established that pain of cardiac origin is transmitted over the sympathetic and not over the vagal afferent fibers. Relief of pain in certain cases of angina pectoris is therefore obtained by injection of alcohol into or removal of the stellate and upper dorsal sympathetic ganglia.

Central Autonomic Connections. There are extensive central ramifications of the autonomic nervous system above the level of the spinal cord. The integration of the control of blood pressure and respiration in the medulla is well known, but there are higher levels of integration of autonomic functions, especially in the hypothalamus and cortex. For example, the *hypothalamus* helps regulate body temperature, blood sugar, water balance, carbohydrate and fat metabolism, blood pressure and sexual reflexes. Much information concerning central influence on autonomic functions has come not only from physiological studies but also from such clinical syndromes as diabetes insipidus, narcolepsy, hypothermia, hyperthermia and diencephalic autonomic epilepsy. The hypothalamic nuclei which lie posteriorly and laterally are sympathetic in their main connections and their stimulation results in massive discharge of the sympatho-adrenal system. Parasympathetic functions are evidently integrated by the midline nuclei in the region of the tuber and by those lying anteriorly. The supraoptic nuclei are also involved in maintenance of water metabolism through their connections with the posterior lobe of the hypophysis. This hypothalamic-pituitary system represents a centrally located autonomic function the peripheral control of which is hormonal in nature.

The *cortex* provides another suprasegmental level of integration for sympathetic and parasympathetic functions. It is mainly here that the correlation between somatic and vegetative functions occurs, both in the sensory and motor fields. The activities of the cardiovascular, gastro-intestinal and many other systems are partially controlled at this highest level, and the basis for conditioned reflexes and visceral processes connected with mental states rests in these cortical connections. For example, sleep itself appears to be essentially a central and peripheral autonomic integration.

The details of the central autonomic nuclei and their control of the peripheral vegetative system must be sought elsewhere (*see* Fulton, 1938, for an excellent review of this subject). Attention is called to these suprasegmental levels of integration because they are often entirely neglected in discussions of autonomic drugs. The actions of these drugs on central nuclei are poorly understood but may be important in determining the character of the body's response. Likewise, the many visceral effects of drugs which stimulate or depress the central nervous system emphasize the significance of central autonomic integrations.

Divisions of the Peripheral Autonomic System. On the motor side, the autonomic nervous system consists of two large divisions—the *sympathetic* (orthosympathetic) or *thoracolumbar* outflow, and the *parasympathetic* or *craniosacral* outflow. The two divisions are quite distinct in many of their anatomical and physiological characteristics. The differences, however, are not absolute and evidence will be presented in a later section to show that certain revisions must be made in the traditional concept that the two systems are always mutually antagonistic.

Only the briefest outline of those anatomical features necessary for an understanding of the actions of autonomic drugs can be given here. The arrangement of the principal parts of the autonomic nervous system is presented schematically in Figure 31, which may be consulted for further elucidation of the following description.

The Sympathetic Nervous System. The cells of this division lie in lateral horns of the spinal cord and extend from the seventh cervical to the third lumbar segment. The anterior nerve roots carry axones from these cells which synapse with neurones lying in certain ganglia outside the cerebrospinal axis. The sympathetic ganglia comprise three groups—the vertebral, prevertebral and terminal.

The *vertebral* sympathetic ganglia consist of 22 pairs which lie on either side of the vertebral column to form two lateral chains. The ganglia are connected to each other by nerve trunks and to the spinal nerves by rami communicantes. The white rami carry the preganglionic medullated fibers from the spinal cord by way of the anterior spinal roots. The gray rami issue from the ganglia and carry postganglionic fibers back to the spinal nerves for distribution to blood vessels of striate muscle and skin and to sweat glands and pilomotor muscles.

The *prevertebral* ganglia serve as synaptic centers. They lie in the abdomen and pelvis on the ventral surface of the bony vertebral column and consist mainly of the celiac (solar), the superior mesenteric and the hypogastric ganglia. The *terminal* ganglia are few in number, lie near the organs which they innervate and consist especially of those connected with the urinary bladder and rectum.

The classic experiments of Langley (page 488) established the course of sympathetic nerve fibers and the sites of their synapses. In this work he utilized the alkaloid nicotine which prevents the response of ganglion cells to preganglionic nerve stimulation. The postganglionic fibers issuing from the sympathetic ganglia reach all the visceral structure of the thorax, abdomen, head, and neck. The trunk and limbs are supplied by means of the sympathetic fibers in the spinal nerves as described heretofore. The prevertebral ganglia contain the cell bodies whose axones supply the glands and smooth muscle of the abdominal and pelvic viscera. Many of the upper thoracic sympathetic fibers from the vertebral ganglia form terminal plexuses such as the cardiac, esophageal and pulmonary. The sympathetic distribution to the head and neck is by way of the cervical sympathetic chain and its three sympathetic ganglia. All postganglionic fibers in this chain arise from cell bodies located in these three ganglia. All preganglionic fibers arise from the upper four thoracic segments of the spinal cord. There are no sympathetic fibers leaving the central nervous system above the first thoracic level.

Each preganglionic fiber issuing from the spinal cord synapses only once. This synapse may occur in any of the ganglia mentioned and need not correspond to the original level of issuance from the spinal cord. Many of the preganglionic fibers from the fifth to the last thoracic segment pass through the vertebral ganglia without synapsing and form the splanchnic nerves. Most of the splanchnic fibers do not synapse until they reach the celiac ganglion. The nerve fibers going to the adrenal medulla are unique in that, although they are preganglionic, they innervate the gland cells directly. The physiological significance of this apparent anomaly will be discussed later.

Parasympathetic Nervous System. This system consists of three outflows of preganglionic fibers from the central nervous system and their postganglionic connections. The regions of central origin are the midbrain, the medulla oblongata and the sacral part of the spinal cord.

The *midbrain* or tectal outflow consists of fibers arising from the Edinger-Westphal nucleus of the *third* cranial nerve and going to the ciliary ganglion in the orbit. The *medullary* outflow comprises the parasympathetic components in the seventh, ninth and tenth cranial nerves. The fibers in the *facial* nerve form the chorda tympani which innervates the ganglia lying on the submaxillary and sublingual glands. They also form the Vidian nerve and innervate the sphenopalatine ganglion. The *glossopharyngeal* autonomic components innervate the otic ganglion. From the aforementioned peripheral ganglia, postganglionic parasympathetic fibers originate which supply the sphincter of the iris, the ciliary muscle and the salivary, lacrimal and mucous glands. These fibers also include the vasodilator nerves to the organs mentioned and the remaining structures of the head. The *vagus* nerves arise in the medulla and consist of preganglionic fibers which do not synapse until they reach the many small ganglia lying directly on or in the viscera of the thorax and abdomen. The preganglionic fibers are thus very long, and the postganglionic quite short. The vagus nerve in addition carries many afferent fibers from the viscera into the medulla.

The *sacral* outflow consists of axones which arise from cells in the second, third and fourth segments of the sacral cord and proceed as preganglionic fibers to form the pelvic nerves. They synapse in terminal ganglia lying near the bladder, rectum, and sexual organs.

The vagal and sacral outflows provide motor, secretory and vasodilator fibers to all the thoracic, abdominal and pelvic organs, as can be seen by reference to Figure 31. The functions of these nerves will be described later.

Difference Between Sympathetic and Parasympathetic Nerves. On purely anatomical grounds, the two divisions of the autonomic nervous system differ in several important respects. Chief among these is the fact that *sympathetic fibers* ramify to a much greater extent. A preganglionic sympathetic fiber may traverse a considerable distance of the sympathetic chain and pass through several ganglia before it finally synapses with a postganglionic neurone. Also, it synapses with a large number of postganglionic fibers. In some ganglia, the ratio between preganglionic axones and ganglionic cells may be one to 20 or more. In this manner, a diffuse discharge of the sympathetic system is possible.

The *parasympathetic system,* on the other hand, has its terminal ganglia very near to the organs innervated and thus is more discrete and limited in its discharge of impulses. In some organs, there appears to be a one to one relationship between the number of parasympathetic preganglionic and postganglionic fibers.

Details of Innervation of Effector Organs. The manner in which autonomic nerve endings make contact with the effector cells is of importance for an understanding of the mechanism of action of autonomic drugs. Unfortunately, histological investigation in this field has yielded only fragmentary information. For example, it is highly desirable to know whether each muscle cell is innervated by a nerve fiber. In the intestinal musculature, it appears that only one muscle cell in a hundred receives a nerve ending. Obviously some other method of stimulation than a direct nerve impulse must exist for those cells which are not innervated. The ciliary muscle of the eye, on the other hand, appears to have a nerve fiber for each muscle cell, but the involuntary ocular muscles are peculiar and possess features common to skeletal muscle. Indeed, in some animals (birds) the iris is composed entirely of striped fibers. In the heart muscle there also appears to be a discrepancy between the number of nerve fibers and muscle cells, but the syncytial nature of the myocardial elements apparently compensates for the lack of abundant nerve fibers.

Whether the nerve ending terminates on the surface of the cell or actually enters the protoplasm is of importance for determining the site of action of autonomic drugs. There is evidence of intracytoplasmic nerve endings in both smooth and cardiac muscle, but the nerve endings of gland cells may be on the cell surface (adrenal, gastric, salivary glands) or within the cytoplasm (hepatic cells).

When an organ is innervated by both sympathetic and parasympathetic nerve fibers, the question arises whether each innervated cell receives fibers from both systems. Although this problem is unsettled, there is no histological evidence at present to warrant the conclusion that both nerve divisions are represented in the same effector cell. It would be more consistent with our knowledge of drug action to have sympathetic fibers supplying certain cells and parasympathetic fibers other cells, but this has not yet been established.

PHYSIOLOGICAL CONSIDERATIONS

Certain physiological aspects of the autonomic nervous system are of importance for the understanding of the action of autonomic drugs.

The Response of Effector Organs to Autonomic Impulses. A clear understanding of the responses of various viscera to autonomic nerve impulses makes it possible to anticipate the actions of neuromimetic drugs. In general, the sympathetic and parasympathetic systems stand as physiological antagonists. If one system inhibits a certain function, the other augments that function. Most viscera are innervated by both divisions of the autonomic nervous system, and the level of activity at any one moment is the result of the algebraic sum of the two component influences. The action of one system is brought into relief by removal or paralysis of the opposing system.

The effects of stimulating the sympathetic and parasympathetic nerves to various organs, visceral structures and effector cells are summarized in Table 17.

General Functions of the Autonomic Nervous System. The integrating action of the autonomic nervous system is of the utmost importance for the well-being of the organism. In general, the autonomic nervous system regulates the activities of structures which are not under voluntary control and which as a rule function below the level of consciousness. Thus respiration, circulation, digestion, body temperature, metabolism, sweating, and the secretions of certain endocrine glands are regulated by the autonomic nervous system and its central connections. As Claude Bernard and Cannon have emphasized, the constancy of the internal

TABLE 17

RESPONSES OF EFFECTOR ORGANS TO AUTONOMIC NERVE IMPULSES

	ADRENERGIC IMPULSES *	CHOLINERGIC IMPULSES *
EYE		
Iris	Mydriasis	Miosis
Ciliary muscle	Relaxed for far vision	Accommodated for near vision
Smooth muscle of orbit	Constricted and exophthalmos	....
HEART		
Rate	Accelerated	Slowed
Output	Increased	Decreased
Rhythm	Ventricular extrasystoles, tachycardia, fibrillation	Bradycardia, A-V block, vagal arrest
BLOOD VESSELS		
Coronary	Dilated	Constricted
Skin and mucosa	Constricted	Dilated
Muscle	Dilated, constricted	Dilated
Cerebral	Constricted	Dilated
Pulmonary	Constricted	Dilated
Abdominal viscera	Constricted	....
LUNG		
Bronchial muscle	Dilated	Constricted
Bronchial glands	Inhibited?	Secretion
STOMACH		
Motility and tone	Decreased	Increased
Sphincters	Contracted as a rule	Relaxed as a rule
Secretion	Inhibited?	Increased, particularly organic constituents
INTESTINE		
Motility and tone	Decreased	Increased
Sphincters	Contracted as a rule	Relaxed as a rule
Secretions	Inhibited?	Increased
GALL BLADDER AND DUCTS	Relaxed?	Contracted
URINARY BLADDER		
Detrusor	Relaxed	Contracted
Trigone and sphincter	Contracted	Relaxed
URETER		
Tone and motility	Decreased	Increased
UTERUS (HUMAN)		
Pregnant	Stimulated	Stimulated
Nonpregnant	Stimulated?	Variable
SKIN		
Pilomotor muscles	Contracted	....
Sweat glands	Secretion (restricted)	Secretion (general)
SPLEEN CAPSULE	Constricted	....
ADRENAL MEDULLA	....	Secretion of epinephrine
LIVER	Glycogenolysis	....
PANCREATIC ISLETS AND ACINI	....	Secretion?
SALIVARY GLANDS	Secretion (sparse, thick, mucinous)	Secretion (profuse, watery)
LACRIMAL GLANDS	....	Secretion
NASOPHARYNGEAL GLANDS	....	Secretion
SKELETAL MUSCLE	....	Stimulated
AUTONOMIC GANGLION CELLS	....	Stimulated

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* The anatomical classes of fibers carrying adrenergic and cholinergic impulses to effector organs are described on page 335.

environment of the organism is to a large extent controlled by the vegetative nervous system. The former investigator used the term *milieu interne* and the latter *homeostasis* to express the concept of the constancy of the internal environment.

The sympathetic and parasympathetic systems, however, have contrasting functions in regulating the internal environment. The *sympatho-adrenal system* is not essential to life, and animals deprived of it can continue a fairly normal existence within the sheltered confines of the laboratory. They grow, become pregnant and give birth to young, although gestation may be abnormal (high incidence of stillbirths), the maternal instinct is absent, and the mammary glands do not secrete. Such animals are also sensitive to cold and their basal metabolic rate is reduced about 10 per cent. They show no tendency toward vagotonia in that the digestive processes are normal, the heart rate is not slowed and the blood pressure is unaltered. Even the peripheral vessels regain a certain degree of intrinsic vasomotor tone. Under circumstances of stress, however, the lack of the sympatho-adrenal functions becomes manifest. In cats, for example, body temperature cannot be regulated when the environment is cold or hot; the blood sugar does not rise in response to urgent need; compensatory vascular responses to hemorrhage, oxygen want, excitement or work do not occur; resistance to fatigue is lessened; instinctive reactions to fright or danger are lost; pilomotor responses are absent, and other serious deficiences in the protective forces of the body are discernible. Dogs, for a number of reasons, withstand complete sympathectomy better than do cats (McDonough, 1939).

The sympatho-adrenal system frequently discharges as a unit and this occurs especially under circumstances of rage and fright (Cannon, 1932). The autonomic structures all over the body are affected at the same time. The heart is accelerated; the blood pressure rises; red blood cells are poured into the circulation from the spleen; the blood redistributes itself from the skin and splanchnic bed to the skeletal muscles; the blood sugar rises; the palpebral fissures widen; the pupils dilate; and, on the whole, the organism is better prepared for fight or flight.

The *parasympathetic system,* on the other hand, is essential to life and is organized for discrete and localized discharge and not for mass responses. It is concerned rather with the functions of conservation and restoration than with the expenditure of energy. It slows the heart, lowers the blood pressure, stimulates the gastro-intestinal movements and secretions, aids absorption, protects the retina from excess light, and empties the bladder and rectum. No useful purpose would be served in the body if the parasympathetic nerves all discharged at once. Indeed, such an event would be harmful.

Cannon (1932) has aptly summarized the distinctions between the two systems as follows, "The sympathetics are like the loud and soft pedals, modulating all the notes together; the cranial and sacral innervations are like the separate keys."

Chemical Mediation of Nerve Impulses

Before proceeding further with physiological considerations, it is necessary to describe certain basic changes that have occurred in our knowledge of the mediation to effector organs of the excitatory process initiated by nerve impulses. This newer information is collectively referred to as the theory of the *"chemical transmission of nerve impulses,"* or *"neurohumoralism."* The theory holds that nerve impulses effect responses in muscles and glands through liberation of a chemical substance which acts as the major local exciting agent. The theory will be outlined in some detail because it has profoundly affected our knowledge of the mechanism and site of action of autonomic drugs.

Historical. The first reference to the possibility that chemical substances might be concerned in the transmission of the excitatory process to effector cells was probably made by Dubois-Reymond who, in 1877, stated that transmission of the nerve impulse may be produced either electrically by action currents or chemically by exciting substances like ammonia or lactic acid formed at the surface of nerve endings. In 1904, T. R. Elliot, while a student of physiology at Cambridge, England, postulated that sympathetic nerve impulses released tiny amounts of an epinephrine-like substance in immediate contact with effector cells. He considered this substance to be the chemical step in the process of stimulation. Elliot's evidence was meager and he was led to this theory by the similarity between the effects of stimulation of sympathetic nerves and the injection of epinephrine. He was also influenced by the fact that long after sympathetic nerves degenerated the effector organs still responded characteristically to the hormone of the adrenal medulla. In 1905, Langely suggested that effector cells have both excitatory and inhibitory "receptive substances," and that the response to epinephrine depended on which type of substance was present.

In 1906, Dixon was so impressed by the correspondence between the effects of the alkaloid muscarine and the responses to vagal stimulation that he advanced the important idea that the vagus nerve liberated a muscarine-like substance which acted as a chemical transmitter of its impulses. Dixon concluded from experimental data that "excitation of a nerve induces the local liberation of a hormone which causes specific activity by combination with some constituent of the end-organ, muscle or gland." Dixon's theory met with universal skepticism which discouraged him from following this promising field of investigation.

In the year that Dixon advanced the above hypothesis, Reid Hunt announced his studies on acetylcholine and other choline esters. In 1914, Dale thoroughly reinvestigated the pharmacological properties of acetylcholine. He was so impressed with the remarkable fidelity with which this drug reproduced the responses to stimulation of parasympathetic nerves that he introduced the term "parasympathomimetic" to characterize its effects. Dale also noted the brief duration of the action of this chemical and believed that an esterase in the tissues rapidly splits acetylcholine to acetic acid and choline, the latter being a much less potent compound.

The Vagus-Substance (Parasympathin). The brilliant researches of Otto Loewi, which were begun in 1921, established the first real proof of the chemical mediation of nerve impulses by the peripheral release of specific chemical agents. Loewi's studies will be described because they are often quoted and the technic he employed is basic to investigations in this field. He stimulated the vagus nerve of a perfused (donor) frog heart and allowed the perfusion fluid to come in contact with a second (recipient) frog heart used as a test object. He noted that a substance was liberated from the first organ which slowed the rate of the second. Loewi called this chemical substance "vagus-substance" (parasympathin). He also discovered that an accelerator substance similar to epinephrine was liberated into the perfusion fluid when the action of the sympathetic fibers in the frog's vagus predominated over the inhibitory fibers.

Loewi's observations were not immediately corroborated by other investigators because of certain technical difficulties. The cardiac nerves from the vagus in frogs also contain the sympathetic accelerator component—the accelerans. The nerve is a mixed one, therefore, and its stimulation at times causes inhibition and at other times acceleration. The particular result varies with the frog and with the season of the year. In winter, inhibition predominates; in summer, acceleration. The exact opposite holds true for the toad. Loewi's discoveries were eventually confirmed and are now universally accepted. The essential features of the experiments are shown in Figure 27 which illustrates Bain's (1932) modification of Loewi's technic.

It was necessary to show that the aforementioned observations also held true for warm-blooded animals with more highly organized nervous systems. In 1927,

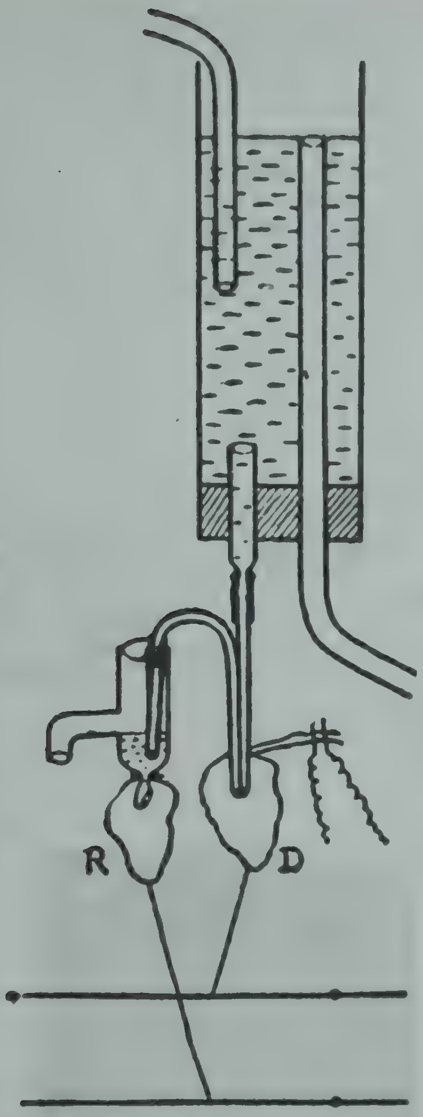
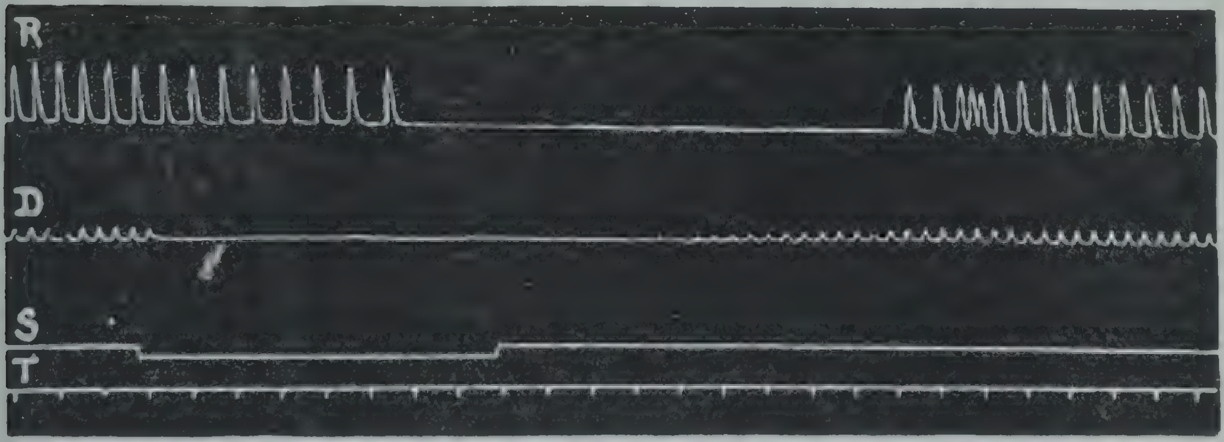


FIGURE 27. *Bain's modification of Loewi's technic for demonstrating the release of the "vagus-substance" upon stimulation of the cardiac nerve to the frog's heart.*

The donor heart (*D*) with nerves intact is perfused at constant pressure with a balanced salt solution. The perfusion fluid then passes to the isolated recipient heart (*R*). Cardiac contractions are recorded by means of writing levers; time (*T*), in five second intervals. The vagus fibers to the donor heart are stimulated (*S*) for 40 seconds, and the donor heart is arrested. Slowing of the recipient heart is apparent within fifteen seconds after arrest of the donor heart and asystole occurs shortly thereafter. (After Bain, 1932. Courtesy of the *Quarterly Journal of Experimental Physiology* and Sir Edward Sharpey Schafer's Trustees.)



Rylant duplicated Loewi's frog experiments using perfused rabbits' hearts. Feldberg and Krayer (1933) extended the field by using intact cats and dogs. They stimulated the cardiac vagus and were able to detect the liberation of the vagus-substance by its effects on eserinized leech muscle and the blood pressure of cats (Figure 28). They presented strong evidence to indicate that the vagus-substance is acetylcholine.

Many other investigations established quite conclusively that a chemical mediator was instrumental in the transmission of excitation not only to the heart but also to other parasympathetically innervated structures. The experiments of Dale and Feldberg (1934) demonstrated the presence of the vagus-substance in the eserinized perfusion fluid collected from the stomach of a dog whose vagi had been stimulated. Similar experiments have demonstrated the chemical transmission of parasympathetic nerve impulses to the small intestine (Bunting, Meek and Maaske, 1935) and to the salivary glands (Babkin and associates, 1932). For example, stimulation of the chorda tympani imparts to the perfusion fluid flowing through the submaxillary gland the power to depress blood pressure, inhibit heart rate, stimulate peristalsis and excite salivary secretion. The work of Engelhart (1931) is of special significance because it shows that the physiological stimulation of nerves also produces the chemical mediator. He demonstrated that impulses over the short ciliary nerves, produced either by electrical stimulation or reflexly by exposure of

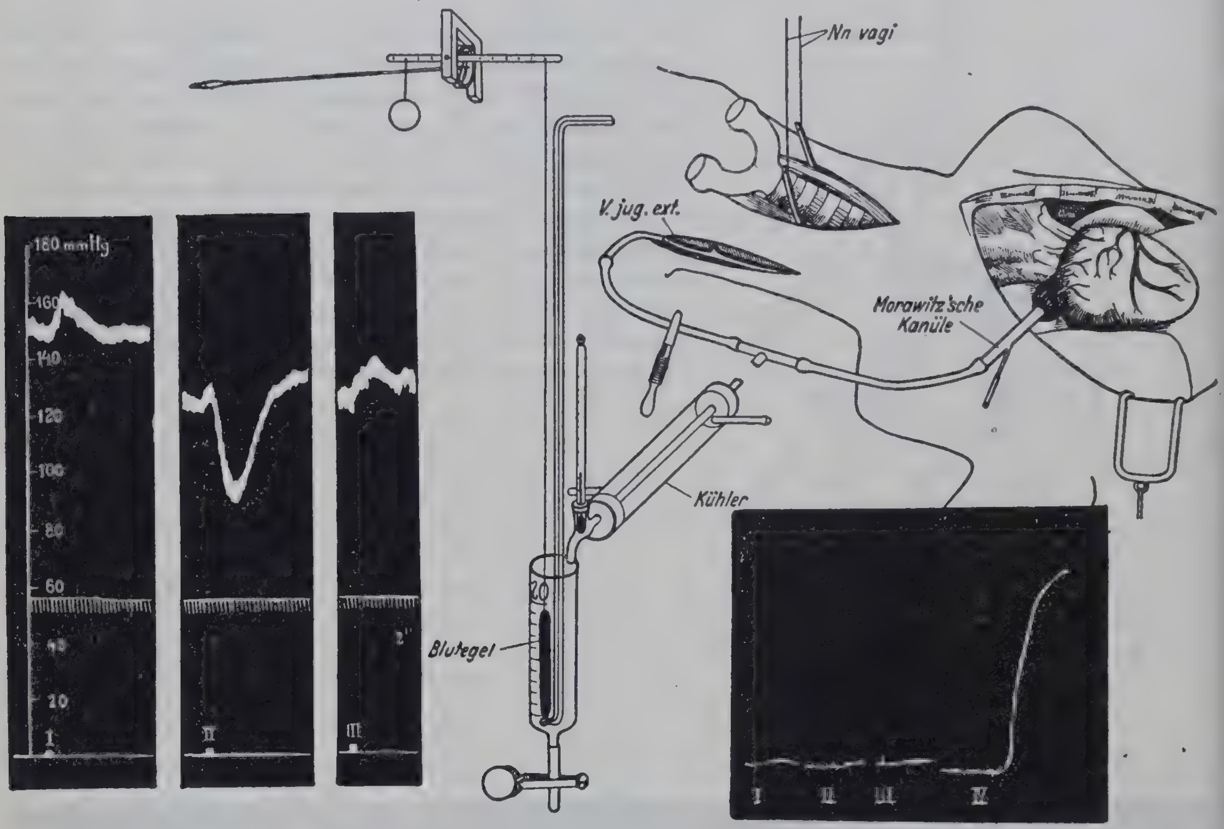


FIGURE 28. *Demonstration of the release of the vagus substance (acetylcholine) in the mammalian heart.*

Schematic representation of exposed dog's heart, vagus nerves and external jugular vein. A Morawitz cannula is inserted into the coronary sinus, from which blood can be diverted at will into a cooling chamber preparatory to testing it on the sensitized leech muscle for its content of acetylcholine. The lower right hand tracings represent responses of the leech muscle to coronary blood obtained under the following circumstances: I, control; II, during vagus stimulation; III, control after eserinization of the dog; IV, during vagal stimulation after eserinization. The carotid blood pressure tracing on the left is that of a cat injected with samples of the dog's coronary blood taken as follows: I, control after eserinization of the dog; II, during vagal stimulation after eserinization. The cat was then atropinized and at III is shown the absence of the vasodepressor response to the same sample of blood used at II. Note that only when the chemical mediator of the vagal impulses is protected by eserine from enzymatic destruction is it possible to demonstrate its presence by the use of appropriate test objects. (After Feldberg and Krayer, 1933. Courtesy of the *Archiv für experimentelle Pathologie und Pharmakologie.*)

the retina to light, liberated a substance which imparted to the aqueous humor the pharmacological properties of acetylcholine. The evidence is overwhelming that stimulation of craniosacral autonomic nerves to muscles and glands results in the release of a chemical which possesses parasympathomimetic properties.

Identification of Acetylcholine as the Vagus-Substance. It is now necessary to digress in order to examine the evidence that the parasympathetic mediator is acetylcholine and to enumerate the pharmacological tests available for detecting its presence in biological fluids.

Acetylcholine can be recognized by a number of fairly specific reactions. The common physiological indicators of its presence and their sensitivity in micrograms per liter (0.001 mgm per liter; 1:1,000,000,000) are given in the following table compiled by Gaddum (1936):

Leech muscle (isolated and treated with eserine)	2
Rabbit auricle (isolated and treated with eserine)	4
Frog heart (Straub method)	10
Mouse intestine	10
Rabbit intestine	20
Frog's rectus abdominis (isolated and eserinized)	20
Cat's denervated gastrocnemius	100

Inasmuch as none of the tests is absolutely specific, certain other criteria must be met in order to establish the identity of the mediator as acetylcholine. These are as follows (Chang and Gaddum, 1933): (1) Eserinization of the test object usually increases the response obtained. (2) The presence of blood or tissue extract decreases or destroys the activity of acetylcholine, and this destruction is prevented by eserine. (3) Acetylcholine is quickly destroyed by hydrolysis in an alkaline medium. (4) Boiling for several minutes in weakly acid solution does not destroy acetylcholine. (5) Atropine, curare and nicotine each block certain definite actions of acetylcholine. (6) The responses to acetylcholine of the various muscle indicators listed bear a definite quantitative relation to each other, and the chemical mediator being studied must give these same relative values before it can be accepted as acetylcholine.

The parasympathetic mediator has fulfilled all the requirements mentioned. Still other reasons for identifying it as acetylcholine (Witanowski, 1925) are that both are dialyzable, soluble in alcohol and not in ether, rendered inactive by an enzyme in blood and tissues (cholinesterase), and restored to activity by acetylation. Also, acetylcholine is the only choline ester that has thus far been chemically identified in animal tissue.

It is believed at present that acetylcholine exists in the tissues in a form which is physiologically inactive, nondiffusible, and insusceptible of destruction by cholinesterase. It would appear that the auricle of the heart, for example, contains more than sufficient acetylcholine to cause cardiac arrest if it were all suddenly changed to an active state. It is of interest that the auricle contains more acetylcholine (and cholinesterase) than does the ventricle, and this may be correlated with the fact that the vagus is distributed mainly to the auricle in the mammalian heart. The change of acetylcholine from an inactive to an active and diffusible form is accomplished by nerve impulses, and it is then susceptible to hydrolytic inactivation by cholinesterase. Nondiffusible tissue acetylcholine persists as long as the parasympathetic nerves remain intact. The ciliary body of the eye, for example, is rich in this substance, but when the ciliary nerve is cut the acetylcholine disappears coincidently with nerve degeneration.

Cholinesterase. The blood and tissues of the body contain a specific enzyme called *cholinesterase* which splits acetylcholine to choline and acetic acid. The choline formed is pharmacologically weak when compared with acetylcholine, having, for example, only 1/100,000 of the vasodepressor potency of its precursor. Cholinesterase appears to exist in tissues especially where acetylcholine is liberated by nerve impulses. The action of the enzyme is rapid and therefore the effect of acetylcholine released by nerve impulses is brief in duration. When cholinesterase is inactivated, however, the action of acetylcholine is prolonged and intensified.

Physostigmine (eserine) and its congeners in low concentration inactivate cholinesterase, and this is the basis for their parasympathomimetic effects. The action of physostigmine on cholinesterase is not one of destruction but merely temporary inactivation, the drug itself being an ester which combines with the enzyme and is slowly hydrolyzed by it. The esterase has all the characteristics of a ferment, and is destroyed by heat at 56 C. and by ultraviolet irradiation.

Attempts have been made to correlate the concentration of serum cholinesterase with various pathological conditions and especially with skeletal muscular dystrophies. No specific disease, as far as can be determined, is characterized by an abnormal concentration of serum cholinesterase, and the only known way markedly to alter the *in vivo* activity of this enzyme is to administer drugs, especially physostigmine and related chemicals.

As will be more fully pointed out when the rôle of acetylcholine in the transmission of the excitatory process in autonomic synapses and neuromuscular junctions is presented, a major criticism which the chemical mediation theory must answer is how acetylcholine released by the nerve impulse is rapidly removed within the brief refractory period of ganglia and skeletal muscles. That cholinesterase exists in tissues in concentrations sufficiently high to destroy the liberated acetylcholine within the refractory period has been shown by the interesting experiments of Nachmansohn and Marnay. In skeletal muscle, the concentration of cholinesterase is several thousand times higher at the motor end plates than in the muscle fibers and the esterasic power of muscle varies directly with its richness of motor end plates (Marnay and Nachmansohn, 1937, 1938). It was calculated by these investigators that 0.000002 μg or 8×10^9 molecules of acetylcholine could be destroyed in five milliseconds by the enzyme present at a single motor nerve ending in a frog's sartorius muscle, and they came to the conclusion that the amount which can stimulate the muscle could easily be destroyed during the refractory period. Later, these observations were extended to the skeletal muscle of the guinea pig, where similar results were obtained. Nachmansohn (1939) also investigated young chickens and mammals (rats and rabbits) and found that the relative richness of embryonic muscle in cholinesterase is associated with the plenitude of nerve elements and almost complete development of end-plates in this tissue. Nachmansohn (1938, 1939) likewise found that a remarkable relationship exists between the amount of acetylcholine which can be split by cholinesterase during the refractory period of effector organs and the amount of acetylcholine liberated by a maximal shock. For example, the enzyme is concentrated in autonomic ganglia (superior cervical) in an amount calculated to be capable of hydrolyzing 2×10^{12} molecules of acetylcholine in one millisecond, or more than sufficient to destroy, within the refractory period of the ganglion, the acetylcholine reported to be liberated by a maximal preganglionic stimulus and capable of causing a postganglionic discharge.

The esterase is much more abundant in the gray matter of the central nervous system than in the white matter. This presumably is due to the presence of cells and synapses in the gray matter. Although the esterasic power varies in different species and in different parts of the cerebrospinal axis, Nachmansohn found it to be quite constant for any one region in any one species. He also noted that the time of appearance of a high concentration of esterase in the embryonic nervous system agreed with the time of the appearance of synaptic function. He suggests that cholinesterase may serve the same function in central synaptic transmission as it does peripherally in ganglia and neuromuscular junctions, that is, the rapid removal during the refractory period of the liberated acetylcholine.

The physiological significance of cholinesterase has been summarized in a review by Nachmansohn (1940).

Sympathin. It has already been stated that Loewi detected an accelerator substance released from frog hearts when the accelerans nerve was stimulated. In the same year, Cannon and Uridil (1921) noted the release from the liver of an epinephrine-like substance upon stimulation of the sympathetic hepatic nerves. This substance increased the blood pressure and heart rate but did not dilate the pupil. Subsequent experiments, mainly by Cannon and his coworkers but also by others, have definitely established that this substance is the chemical mediator of the excitatory process initiated by sympathetic nerve impulses in neuroeffector junctions. The mediator has been called "sympathin" by Cannon in order to avoid premature implications regarding its exact chemistry.

Just as there are biological indicators for the presence of acetylcholine, so also there are specific test objects for detecting sympathin. The test objects are denervated effector organs, and the responses consist of acceleration of the heart rate, elevation of blood pressure, erection of the hairs, inhibition of intestinal musculature, relaxation of the non-pregnant cat uterus, stimulation of the retractor penis, decrease in size of the spleen, and retraction of the nictitating membrane of the cat.

With the use of these tests, it has been repeatedly demonstrated that when sympathetic nerves, with a few exceptions to be mentioned later, are stimulated there is released a chemical substance which has sympathomimetic properties. For example, Rylant (1927) extended Loewi's amphibian observations to rabbit hearts. Again, Bacq (1931, 1933) found that stimulation of the cervical sympathetic nerves caused sympathin to appear in the aqueous humor of the eye. Sympathin is not only liberated under experimental circumstances but is also produced in the intact animal, as during struggle or excitement. It is likewise formed during sham-rage in decorticate animals. The numerous other experiments of this nature and the progressive steps by which Cannon and his associates developed the concept of sympathin can be found in the reviews of this subject (Cannon and Rosenblueth, 1937; Rosenblueth, 1937).

The Nature of the Sympathetic Mediator: Sympathin E and I. In many of its pharmacological properties and perhaps also in chemical structure, sympathin bears close resemblance to epinephrine. Both epinephrine and sympathin are enhanced in their activity by cocaine and by nerve degeneration. Both substances are inactivated by exposure to air for twenty-four hours, by boiling, by strong alkali, and by eosine and ultraviolet light. Both give the same color reactions (Viale color reaction, and green fluorescence with strong alkali and oxygen), the same qualitative ultraviolet absorption spectra of the polyphenols, and show similar variations in absorption as the pH is changed.

Sympathin, however, differs from epinephrine in certain important respects. Epinephrine has both excitatory and inhibitory effects when injected into the body. Thus it accelerates the heart but inhibits the intestine. Sympathin, in contrast, has these two actions, but they are separable. For example, stimulation of a sympathetic nerve supplying a region where there are structures both excited and inhibited by sympathetic impulses produces sympathin which possesses both augmentative and inhibitory properties. When nerves causing only excitatory responses are stimulated, the sympathin released possesses only augmentative activity. This excitatory form of sympathin also differs from epinephrine in failing to stimulate the dilator muscle of the iris. Perhaps the greatest contrast between sympathin and epinephrine is seen in their action after ergotoxine. Whereas ergotoxine blocks the rise of blood pressure produced by epinephrine, it does not prevent that caused by sympathin.

These facts led Cannon and Rosenblueth (1933) to postulate the existence of two forms of sympathin known as sympathin E (excitatory) and sympathin I (inhibitory). The theory holds that a chemical mediator (M) is released at sympathetic nerve endings and combines in effector cells with a hypothetical substance (H). The nature of the H substance depends upon whether the effector cell is excited (E) or inhibited (I) by nerve impulses. It is the combination of M and H which causes the characteristic response of the effector cell, and the MH can therefore be of two varieties, ME and MI. The sympathin released into the blood stream from the effector cell bears the characteristics of this MH combination. If the effector cell was inhibited by nerve stimulation, the sympathin will be inhibitory in nature and is called sympathin I. If the effector cell was excited, the sympathin coming away from it will cause excitation and is called sympathin E. Thus, sympathin E would be formed in the heart and blood vessels, and sympathin I in the intestine, urinary bladder, bronchi, etc. (Figure 29).

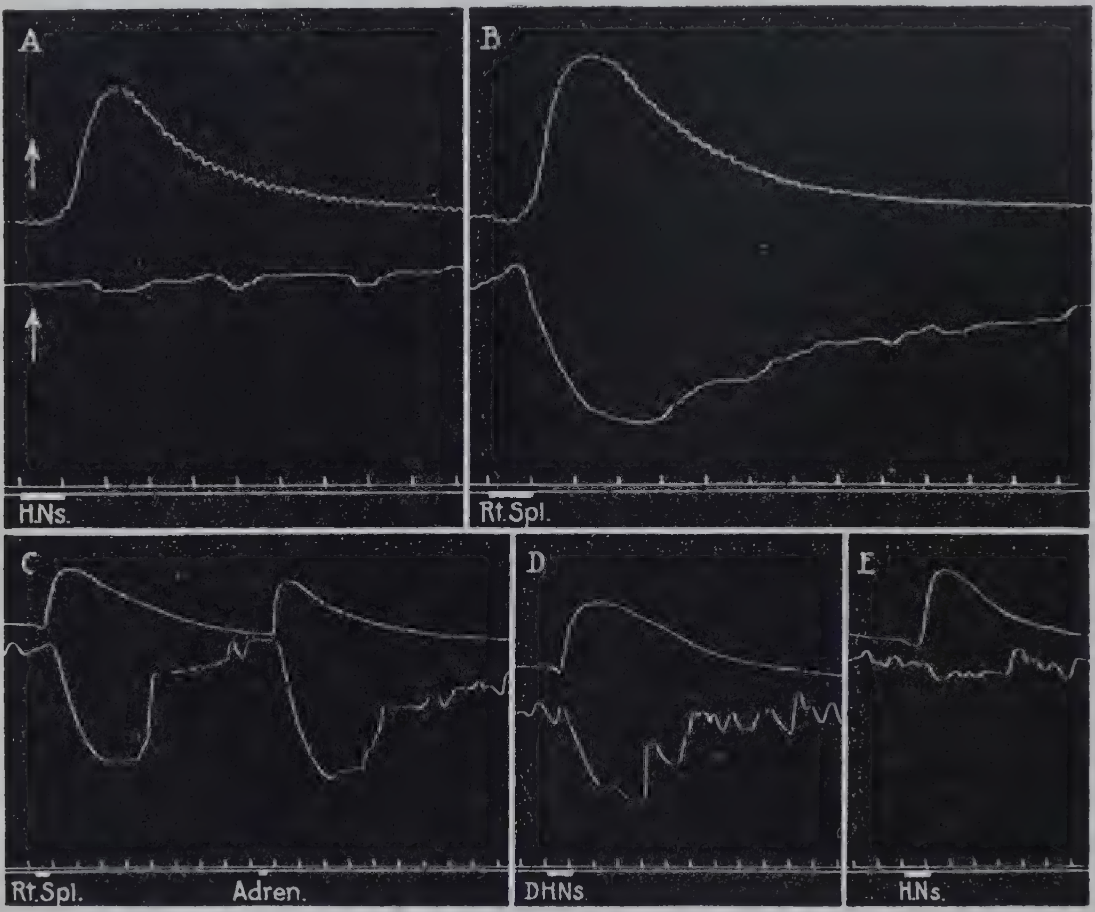


FIGURE 29. *Effects of sympathin from excited* (E) *and inhibited* (I) *sources in the cat on indicators which contract or relax.*

In each instance the upper record is that of the nictitating membrane with cervical sympathetic nerve cut (indicator for sympathin *E*); the lower record, that of the denervated nonpregnant uterus (indicator for sympathin *I*). Direction of arrows indicates contraction. Time is given in half-minutes. *A.* Effects of stimulating the hepatic nerves (*H. Ns.*), purely excitatory. *B.* Effects of stimulating the right splanchnic nerves (adrenals excluded), excitatory and inhibitory. *C.* Effects of stimulating the splanchnic nerves (adrenals excluded) are similar to those of injecting epinephrine (0.3 cc of 1:200,000). *D.* Effects of stimulating the duodenohepatic nerves (*D. H. Ns.*), excitatory and inhibitory. *E.* After severance of the duodenal nerves (excitatory and inhibitory), stimulation of the hepatic nerves (*H. Ns.*), excitatory only. (After Cannon and Rosenblueth, 1933.)

There have been many objections to and modifications of the theory of two sympathins, and these have been reviewed by Cannon and Rosenblueth (1937). For example, sympathin I has not yet been shown to exist alone, but this is probably due to the fact that there is no organ in the body inhibited by sympathetic impulses which does not also contain some excitatory fibers to blood vessels. It has been suggested that the two sympathins are only chemical modifications of epinephrine and are not produced as such in the effector cells. Despite the many criticisms and objections, it seems that no other explanation so well fits all the experimental observations.

Acetylcholine as the Transmitter of Impulses of Certain Postganglionic "Sympathetic" Fibers. It has long been known that the responses to drugs of sweat glands and certain vascular beds (especially in the skin of the face) presented unexplainable anomalies. The sweat glands are innervated by nerve fibers which belong anatomically to the postganglionic sympathetic system, but their function is nevertheless modified by parasympathetic drugs. A similar situation holds true for blood vessels in certain cutaneous areas, although here there is evidence that the vasomotor nerves may be posterior root fibers and anatomically related to the parasympathetic system (*see* discussion by Fulton, 1938). Dale and Feldberg (1934) have demonstrated that nerve impulses which cause vasodilatation and sweating are mediated by acetylcholine and that the nerves involved are functionally analogous to parasympathetic postganglionic nerves. The mechanism of action of autonomic drugs on sweat glands and blood vessels is considerably clarified by this interpretation.

Chemical Mediation in Autonomic Ganglia. The concept of transmission of the excitatory state initiated by nerve impulses in smooth muscle and gland cells by chemical mediators has been extended from the domain of peripheral autonomic effector organs to embrace the autonomic ganglia. The theory holds that the excitation of the ganglion cells is accomplished by the release of a chemical agent when the preganglionic nerve impulse reaches the synapse. The chemical mediator has been identified as acetylcholine. Although the evidence supporting this view has been obtained from sympathetic ganglia, due to their more ready anatomical accessibility, there are many collateral data to suggest that the same mediator is operative in parasympathetic ganglia. In its simplest form, therefore, the theory holds that all preganglionic nerve impulses, whether sympathetic or parasympathetic, stimulate ganglionic cells through the intervention of acetylcholine released at the synapse.

The aforementioned theory is called the Kibjakow-Feldberg theory of ganglionic chemical transmission, after the investigators who were the first to present evidence in this field (Kibjakow, 1933; Feldberg and Gaddum, 1934; Feldberg and Vartiainen, 1934). In brief, the experiments are based on isolating and perfusing a sympathetic ganglion (usually the superior cervical) and testing the perfusate for acetylcholine after stimulation of the preganglionic fibers. According to a number of investigators (*see* MacIntosh, 1939), the mediator appears in the perfusion fluid only after preganglionic and not after antidromic stimulation, and is not liberated spontaneously in the absence of preganglionic stimulation. The ganglionic cells can be discharged by injecting small amounts of acetylcholine into the perfusion fluid or blood supply to the ganglion. The potentiative action of physostigmine on preganglionic stimuli, as shown by Rosenblueth and Simeone (1938), also supports the view that acetylcholine is the transmitter.

Experiments of several types indicate that the ability of preganglionic impulses to discharge ganglion cells and to release acetylcholine into ganglionic perfusates go hand in hand. For example, Kahlson and MacIntosh (1939) have demonstrated that when Locke's solution without glucose is perfused through a sympathetic ganglion, continued stimulation of the preganglionic nerve rapidly exhausts the mechanism of synaptic transmission. The output of acetylcholine from the ganglion simultaneously fails. Both are restored at the same time when glucose, lactate or pyruvate is added to the perfusion fluid. When Locke's solution lacks calcium, Harvey and MacIntosh (1940) have shown that the ganglion cells become more excitable especially to potassium ions, but that synaptic transmission and the release of acetylcholine by preganglionic nerve impulses fail together. Both are promptly and simultaneously restored by adding calcium to the perfusion fluid. Also, MacIntosh (1938) found that after preganglionic nerve section, synaptic transmission and the release of acetylcholine by preganglionic nerve impulses disappeared together, at a time when conduction is still unimpaired in the cut fiber. Collateral evidence of a major or important adjuvant action of acetylcholine in synaptic transmission in ganglia has also been presented by Bronk and associates from a study of the effects on postganglionic nerve responses obtained by perfusing ganglia with low concentrations of acetylcholine (*see* Bronk, 1939). Impressive evidence therefore exists to suggest that acetylcholine, released at ganglionic synapses by preganglionic nerve impulses, plays an important rôle in the transmission of the excitatory process to ganglion cells.

Chemical Mediation of Impulses Causing Secretion of Epinephrine. The cells of the adrenal medulla are innervated through the splanchnic nerves by preganglionic sympathetic fibers coming directly from the central nervous system (Figure 31). Ordinarily, peripheral autonomic structures are not innervated by preganglionic fibers. The anomaly of the adrenal medulla, however, is explainable on an embryological basis, because the cells which secrete epinephrine are modified neuroblasts and are anatomically homologous with sympathetic ganglion cells. Therefore the splanchnic innervation of the adrenal medulla is characteristic of that of an autonomic ganglion. Acetylcholine is thus the mediator of nerve impulses causing the secretion of epinephrine. When the splanchnic nerves are stimulated in an eserinized animal, it is possible to detect acetylcholine as well as epinephrine in the venous blood coming from the gland. Furthermore, acetylcholine is a powerful direct stimulant of the secretion of epinephrine.

Chemical Mediation in Skeletal Muscle. One of the most provocative and significant advances in the field of chemical transmission of nerve impulses has been the demonstration that motor impulses of somatic nerves to skeletal muscles mediate their effects by means of acetylcholine. Thus acetylcholine may not be confined to the autonomic system alone and, if such is the case, some of the traditional differences between the autonomic and somatic nervous systems become less rigid. Dale, Feldberg, Brown and their collaborators have demonstrated that when the motor nerve to skeletal muscle is stimulated under proper experimental conditions acetylcholine can be recovered from the perfusion fluid (Figure 30). The injection of as little as two micrograms of acetylcholine into the artery of a muscle properly prepared and isolated will cause a quick twitch-like contraction which reproduces in many details the type of response obtained from electrical stimulation of motor nerves.

The action of physostigmine on this response as well as the effect of denervation (page 344) are compatible with the theory of chemical mediation in skeletal muscle. Curarine annuls the response of skeletal muscle to injected acetylcholine and to nerve impulses simultaneously without affecting the response to potassium ions or interfering with the release of acetylcholine by the motor nerve impulses (Dale, Feldberg and Vogt, 1936; Brown, Dale and Feldberg, 1936). Buchtal and Lindhard (1939) confirmed these observations by applying curarine under microscopic control directly to the motor end-plate of a lizard's muscle fiber. They noted that the muscle cell simultaneously became insensitive to motor nerve impulses and to the application of acetylcholine, but that the end-plate remained excitable to direct electrical stimulation and to potassium ions, both of which were still normally effective in eliciting a contraction of the muscle fiber.

Although many details of this complex problem require elucidation, it would appear that minute amounts of acetylcholine are liberated at motor nerve endings in skeletal muscle, are concerned with the transmission of the excitatory process across the neuromuscular junction, and initiate the changes which result in muscular contraction (Dale, 1939).

Temporal and Quantitative Aspects of Chemical Transmission in Autonomic Ganglia and Skeletal Muscles. One of the main objections to the theory of chemical transmission of the excitatory process in autonomic ganglia and skeletal mus-

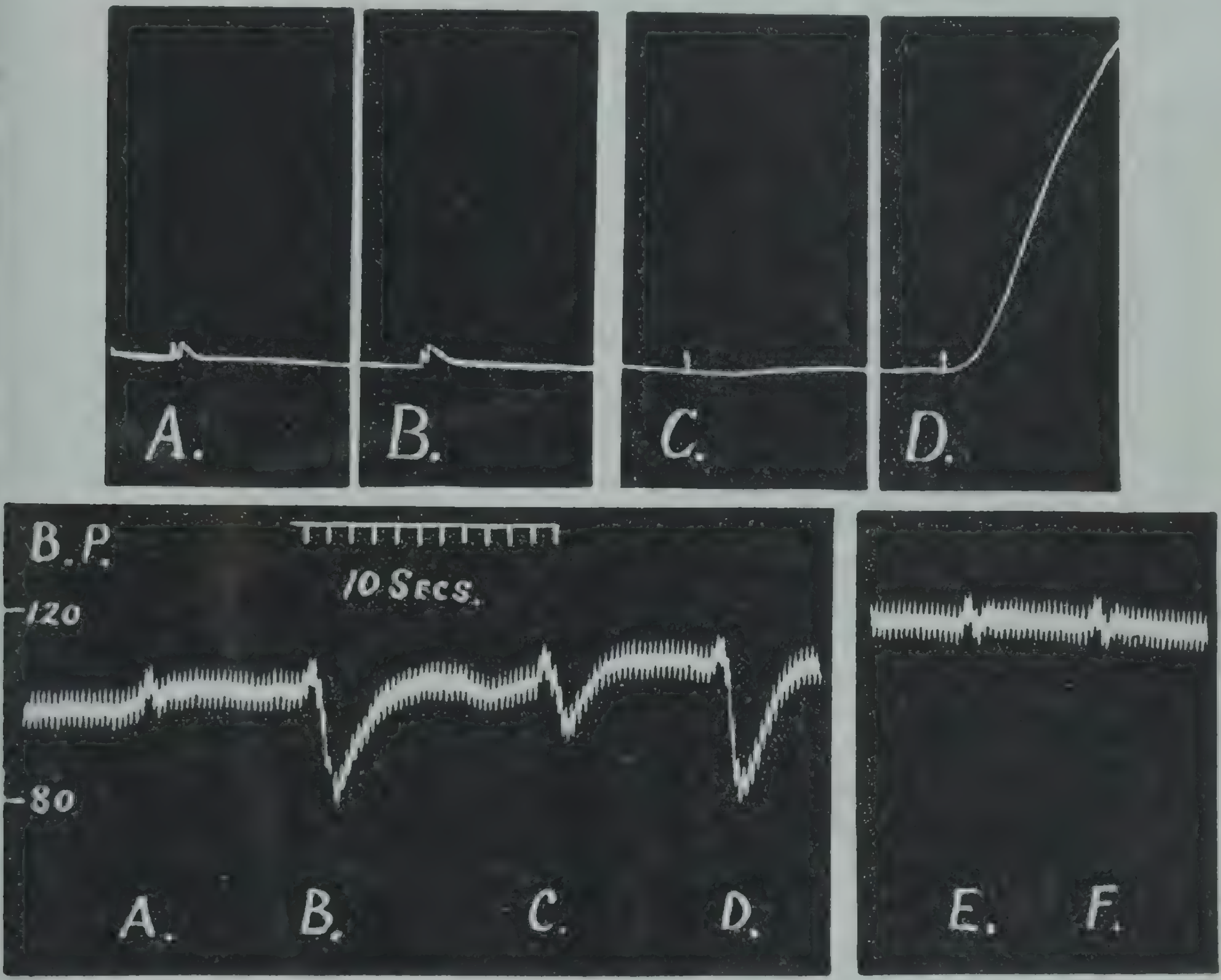


Figure 30. *Acetylcholine as the mediator of motor nerve impulses to skeletal muscles.*

Above: Responses of the sensitized leech muscle to diluted eserinized venous fluid obtained from perfusion of the cat's gastrocnemius muscles. *A.* Control fluid from resting denervated muscle. *B.* Fluid obtained while the muscle was contracting vigorously in response to direct electrical stimulation. In neither case was a contraction of the leech muscle observed, the small rise in the curve being an accidental mechanical effect. *C.* Control fluid from normally innervated muscle. *D.* Fluid obtained during stimulation of the motor nerve to the muscle.

Below: Response of the carotid blood pressure of a cat to venous fluids obtained from the perfused tongue of an eserinized donor cat under curare. *A.* Control fluid obtained before stimulation of the hypoglossal nerve. *B.* Fluid obtained during motor nerve stimulation. *C.* and *D.* Injection of two cc of acetylcholine in dilutions of 1 in 2 x 10^8 and 1 in 10^8, respectively. *E* and *F.* Same as *B* and *D,* after atropinization of the test cat.

Observe that the presence of the chemical mediator of the motor nerve impulses to skeletal muscles can be demonstrated by the responses of suitable test objects when eserine is employed to protect the mediator from destruction, that it is produced only in innervated muscles during stimulation of motor nerves, and that curare does not prevent its release. (After Dale, Feldberg and Vogt, 1936. Courtesy of the *Journal of Physiology.*)

cles has come from the fact that it is necessary to account for the time relations between nerve stimulation and cell response if the mediator is a chemical substance. In the case of peripheral autonomic effector cells, such as the response of the heart or intestine to vagal stimulation, the delay between stimulation and reaction is sufficiently long to be compatible with the theory of chemical transmission. In the case of the heart, for example, the lag may amount to 100 milliseconds which provides ample time for the liberation, diffusion, action and destruction of a chemical mediator. Even the persistence of effects after cessation of stimulation can be accounted for in this way. In ganglia, however, the very short synaptic delay is two milliseconds or less. This would necessitate that acetylcholine be released in minute yet effective amounts and be destroyed almost immediately with "flash-like suddenness," as Dale has expressed it.

The objections to the chemical mediation theory as applied to ganglia have been well reviewed by Eccles (1936, 1937). It is claimed by some workers that there are two types of mediators of nerve impulses—the slow (chemical) and the rapid (electrical). They contend that transmission in ganglia requires the rapid type and that chemical transmitters are concerned only with certain but not all aspects of smooth muscle stimulation. Many of the characteristics and problems of synaptic transmission have been reviewed in a symposium on the synapse by Bronk (1939), Erlanger (1939), Forbes (1939) and Lorente de Nó (1939).

Despite the objections enumerated, the data in favor of the chemical theory, though not complete, are impressive. The evidence for chemical transmission in ganglia is probably as strong as, or stronger than that available for the transmission by acetylcholine of nerve impulses to peripheral effector cells (Brown, 1937). There are several lines of indirect evidence which support the chemical theory as applied to ganglia. These have to do with regeneration of cross-sutured nerves (page 335), the action of potassium salts, nicotine, eserine and other drugs on ganglia (page 331), sensitization of ganglia to acetylcholine after degeneration of preganglionic fibers (page 344), and the responses of skeletal muscles to drugs (page 341). Nevertheless, further information concerning the quantitative and temporal features of acetylcholine-cholinesterase relationships in biological systems is urgently required. The promising investigations of Nachmansohn already described suggest that the esterase concentrations at neuro-effector junctions are sufficiently high to destroy, within the refractory period of the effector cells, amounts of acetylcholine which have stimulating effects. More data of this type are necessary.

Chemical Mediation of Central Synaptic Transmission. A number of workers who most vigorously support the acetylcholine theory of chemical transmission of the excitatory process initiated by nerve impulses in ganglia and skeletal muscles are inclined to believe that it may be possible to demonstrate chemical mediators in the central nervous system essential for synaptic transmission. The evidence for the rôle of a chemical mediator in central transmission is as yet meager. The details should be sought in the reviews listed at the end of the chapter. Particularly noteworthy are the investigations of Nachmansohn on the esterasic power of various portions of the cerebrospinal axis. The pharmacological studies of Schweitzer and Wright on the effect of acetylcholine and anticholinesterase drugs on the functions of the central nervous system are likewise pertinent (pages 379–380). In addition, Mann, Tennenbaum and Quastel (1938) have shown that nervous tissue alone is capable of synthesizing acetylcholine *in vitro*. The observations of Haimovici and Cannon (page 344) that partly denervated spinal cord neurones become sensitized to acetylcholine and strychnine are highly suggestive, and Nachmansohn has demonstrated that strychnine is capable of inhibiting cholinesterase *in vitro* in concentrations which *in vivo* are capable of causing convulsions (page 258). Furthermore, Chute, Feldberg and Smyth (1940) observed that acetylcholine in significant amounts was released into the perfusion fluid flowing through the isolated cat's brain. Finally, it may be mentioned that Miller and coworkers (1940) demonstrated by use of the electrocorticogram that eserine

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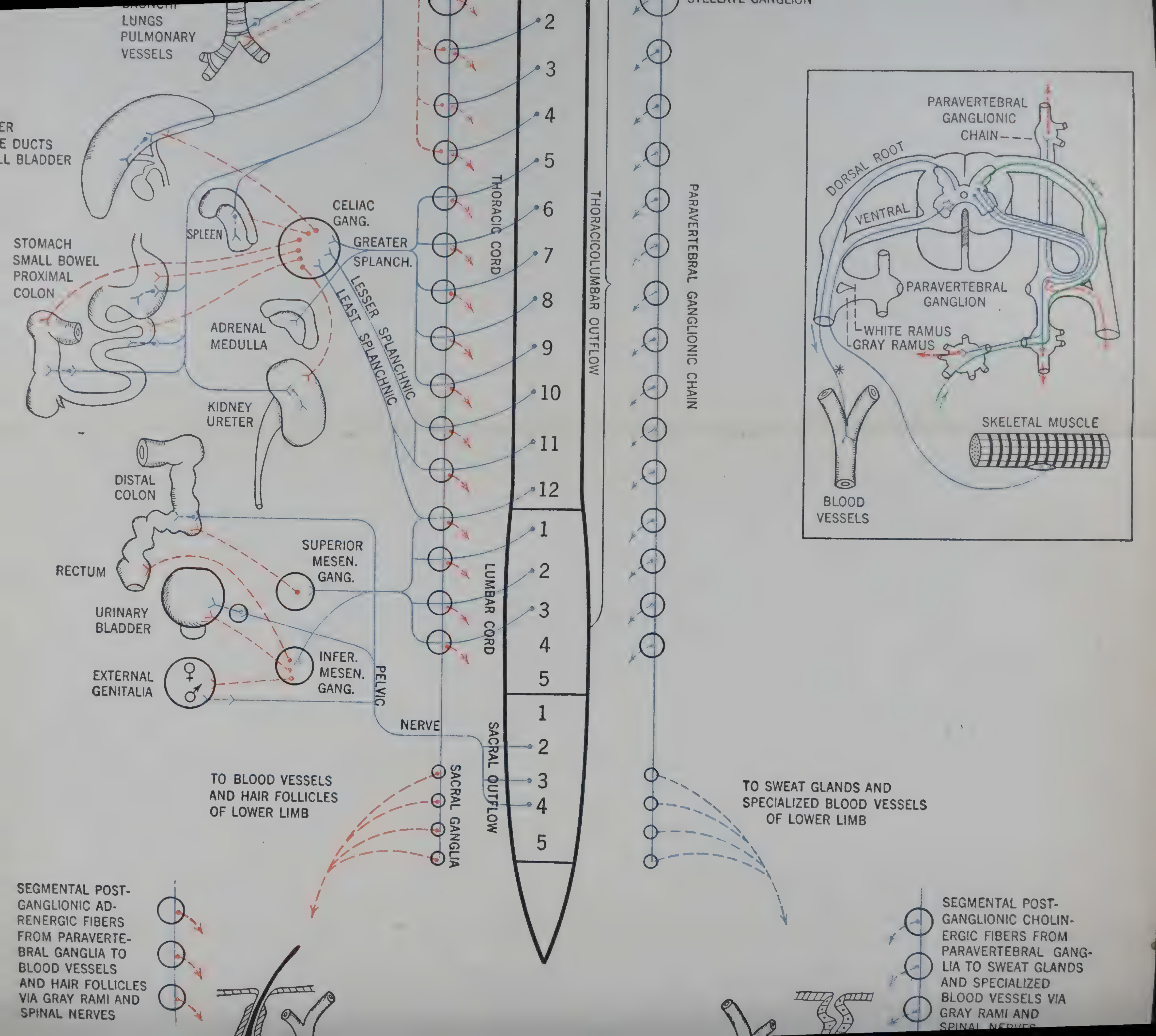
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THORACICOLUMBAR OUTFLOW
PARAVERTEBRAL GANGLIONIC CHAIN
TO BLOOD VESSELS
AND HAIR FOLLICLES
OF LOWER LIMB
TO SWEAT GLANDS AND
SPECIALIZED BLOOD VESSELS
OF LOWER LIMB
PARAVERTEBRAL
GANGLIONIC
CHAIN
DORSAL ROOT
VENTRAL
PARAVERTEBRAL
GANGLION
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GRAY RAMUS
SKELETAL MUSCLE
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FROM PARAVERTE-
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AND HAIR FOLLICLES
VIA GRAY RAMI AND
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ERGIC FIBERS FROM
PARAVERTEBRAL GANG-
LIA TO SWEAT GLANDS
AND SPECIALIZED
BLOOD VESSELS VIA
GRAY RAMI AND

stimulated the motor cortex of cats and that acetylcholine produced similar stimulation but to a lesser degree. When acetylcholine was applied to the eserinized cortex, large stimulatory spikes were produced similar to those evocable by strychnine. The above are but a few of the suggestive lines of research which point to the possibility of chemical mediation of central synaptic transmission.

Chemical Classes of Nerves. The demonstration that acetylcholine acts as the chemical transmitter of impulses for nerves other than postganglionic parasympathetic nerves suggested to Dale the necessity of a new terminology which would classify nerves not anatomically but physiologically. He therefore proposed the terms "cholinergic" and "adrenergic" as functionally descriptive terms which designate the type of chemical activity by means of which nerve impulses transmit the excitatory process to effector organs.

Cholinergic Nerves. These include all nerves which release acetylcholine at their terminals. The category encompasses not only all postganglionic parasympathetic fibers, but also all autonomic preganglionic nerves, whether sympathetic or parasympathetic, the splanchnic (preganglionic) fibers to the adrenal medulla, the "sympathetic" fibers to sweat glands and certain blood vessels, and the somatic motor nerves to skeletal muscles.

Adrenergic Nerves. These include all nerves whose impulses act through the release of an epinephrine-like substance (adrenine; sympathin) and consist only of postganglionic sympathetic fibers. In Figure 31 are illustrated the main cholinergic and adrenergic nerve distributions in the body.

Nerve Regeneration. The experimental and clinical work on cross-suturing of nerves has demonstrated some interesting compatibilities and incompatibilities which, prior to the chemical mediation theory, were quite unexplainable. If one reviews this field in the light of chemical classes of nerves (Dale, 1935), it becomes apparent that cholinergic nerves can be cross-sutured to each other and establish functional union with effector end-organs or ganglia. Adrenergic nerves can be similarly interchanged with each other and establish functional contact with end-organs. Cholinergic fibers, however, cannot be united with adrenergic fibers and the two systems are mutually exclusive. This explains why even motor fibers to skeletal muscle can regenerate down the path of resected preganglionic autonomic nerves or postganglionic parasympathetic nerves and reestablish functional innervation of denervated structures. Also preganglionic autonomic nerves can make functional union with skeletal muscles when united to somatic motor nerves. The implications of these conclusions for the neurosurgeon are of the highest importance.

Autonomic Organization and Chemical Mediators. Under the discussion of anatomical organization of the autonomic nervous system, it was emphasized that the sympathetic nervous system is constructed for mass discharge as contrasted with the organization of parasympathetic nerves for discrete discharge. Also, under the discussion of the functions of the two systems, the rôle played by each in the economy of the organism was summarized. It is now possible to correlate this information with the existence of chemical mediators and chemical classes of nerves.

The sympathetic nervous system is anatomically organized so that one preganglionic fiber can make contact with a score or more of postganglionic fibers and thus greatly increase the area of distribution of nerve impulses. In addition, sympathetic nerve impulses are reinforced by epinephrine released from the adrenal medulla and by sympathin. The latter diffuses from structures receiving adrenergic innervation to circulate in the blood and affect distant organs. Both sympathin and epinephrine may exert their influence for many minutes and no drug analogous to eserine is necessary to protect them from destruction in the body. The parasympathetic nervous system is not only anatomically restricted to localized discharge, but the acetylcholine produced at cholinergic nerve endings is rapidly destroyed by the cholinesterase of the tissues and blood. Therefore it cannot circulate to distant parts. Furthermore, there is no special gland for the production of acetylcholine in the body as there is for epinephrine. It is these factors which allow the two divisions of the autonomic nervous system to function each in its characteristic manner in controlling the constancy of the internal environment of the body.

PHARMACOLOGICAL CONSIDERATIONS

The physiological advances outlined in the preceding pages have naturally had their parallel in the field of pharmacology, and it is desirable at this point to correlate these two phases of the subject. The concept of chemical mediation of nerve impulses, especially as applied to ganglia and skeletal muscles, has probably raised more problems in physiology than it has solved. This generally happens when new facts profoundly change old conceptions. It must be admitted that many aspects of the subject remain open for subsequent revision. The complexity of the problems involved makes it highly probable that our present ideas will require modification as investigations proceed. An acceptance of the hypothesis of chemical transmission, however, does not imply that one must discard all the older concepts concerning the nerve impulse. For the pharmacologist, at least, the theory of the intervention of chemical mediators at neuro-effector junctions, in whatever form they may be associated with the transmission of the excitatory process, allows a much clearer understanding of the actions of autonomic drugs, many of which were formerly classified purely as anomalies. When considered in the light of the chemical mediation theory, the complex and multiple actions of autonomic drugs lend themselves to an orderly, plausible and clinically fruitful interpretation.

Classification of Autonomic Drugs. Drugs acting on structures innervated by autonomic nerves either stimulate or depress the functions of effector cells. The older classification correlated these actions with the two anatomical divisions of the autonomic nervous system. Thus autonomic drugs were grouped as sympathetic stimulants and depressants, and parasympathetic stimulants and depressants. Such a division does not take into consideration the chemical classes of nerves, ganglionic sites of drug action, or somatic structures which respond to autonomic drugs.

With slight changes in the older classification, it is possible to group autonomic drugs in such a manner as to indicate their relation to each other and their sites of action. In order to do this, it is first necessary to have clearly in mind the fact that the drugs stimulate or depress effector cells and not nerve endings. A second point, which must be accepted provisionally and for which more evidence will be presented later, is that skeletal muscle cells respond to a number of autonomic drugs in the same manner as do autonomic ganglion cells, and that the cholinergic somatic motor nerves supplying such muscle cells are in some important respects quite analogous to cholinergic nerves supplying autonomic ganglia. With these facts in mind, autonomic drugs may be classified as in Table 18.

Site of Action of Autonomic Drugs. The older concept that the nerve terminals or endings were stimulated or depressed by drugs had to be abandoned when it was demonstrated that responses could be obtained even after complete denervation, or in embryonic structures before nerves had grown into the organ. The terms "myoneural junctions" and "receptive substances" were then used to indicate the hypothetical part of effector cells on which drugs were thought to act. In the opinion of some authorities (Loewi, 1936), it is highly doubtful whether these terms are any longer serviceable. It is claimed that autonomic drugs and chemical transmitters probably act directly on the effector cell, and that if the action of a drug is on some specific part of the cell, that part is probably not differentiated histologically but only physicochemically from the remainder. Other workers (Cannon and Rosenblueth, 1937) believe that inasmuch as the contractile substance is probably identical in all smooth muscle cells, there must be some differentiating substance in the muscle which is separate from the contractile material, and which determines whether contraction or relaxation occurs. For example, epinephrine relaxes the intestinal musculature, and acetylcholine contracts it. Furthermore, both acetylcholine and epinephrine cause contraction in some muscles, relaxation in others. It is therefore claimed that it is necessary to assume the existence of some differentiating substance which determines the particular responses, such as the H substance referred to under the discussion of the sympathins. Years ago, Langley found it necessary to hypothecate the presence of a "receptive substance" to explain these phenomena, and this expression is still employed.

TABLE 18

DRUGS ACTING ON CELLS INNERVATED BY:

	PREGANGLIONIC CHOLINERGIC NERVES*	POSTGANGLIONIC CHOLINERGIC NERVES**	ADRENERGIC NERVES†
Stimulants	Acetylcholine Acetylbetamethylcholine Carbaminoylcholine Other choline esters Physostigmine (eserine) †† Prostigmine ††	Acetylcholine Acetylbetamethylcholine Carbaminoylcholine Other choline esters Physostigmine (eserine) †† Prostigmine ††	Epinephrine Ephedrine Benzedrine Other sympathomimetic amines
	Nicotine	Pilocarpine Muscarine Arecoline	
Depressants ("Autonomic Blocking Agents")	Nicotine (mainly on ganglia) Curare (mainly on skeletal muscle) Acetylcholine (high concentrations) Physostigmine group ††	Atropine Scopolamine Hyoscyamine Homatropine	Ergotoxine Ergotamine Dioxane derivatives and sympatholytic agents

* Includes all preganglionic parasympathetic and sympathetic nerves, and all cerebrospinal somatic nerves to skeletal muscles (see text).

** Includes all postganglionic parasympathetic nerves, and certain sympathetic nerves to sweat glands and blood vessels.

† Includes all postganglionic sympathetic nerves except those to sweat glands and certain vascular beds.

†† These drugs act indirectly on cells by preventing cholinesterase from destroying acetylcholine.

(After Goodman, 1940)

Newer Concepts of Drug Actions. As Dale (1935) has pointed out, it is no longer correct to say that *acetylcholine* and *epinephrine* reproduce effects of parasympathetic and sympathetic nerves, but "it is truer to say that parasympathetic and sympathetic nerve impulses reproduce the peripheral effects of acetylcholine, because when they arrive at the nerve-endings, they liberate that substance in relation to the effector cells; and the same is true of the sympathetic nerve impulses . . ." Thus while it may be convenient descriptively to speak of pilocarpine, for example, as parasympathomimetic and ephedrine as sympathomimetic, it is not permissible so to label acetylcholine and epinephrine, which supply in themselves the chemicals liberated by autonomic nerves.

The autonomic drugs act on cells and not on nerve endings. Without describing the pharmacology of these drugs, it is necessary at this point to place their site of action more accurately in relation to the *sequence of events by which nerve impulses lead to responses in effector cells.* This sequence can be presented in the following scheme which, although incomplete, will serve present purposes:

1. Preganglionic nerve impulse.
2. Liberation of chemical mediator (acetylcholine) in ganglia.
3. Postganglionic nerve impulse.
4. Liberation of chemical mediator (acetylcholine or sympathin) at end-organ.
5. Combination of mediator with "receptive substance."
6. Specific response of muscle or gland.

Acetylcholine. The relation of this chemical to the mediation of nerve impulses has already been discussed. It functions at steps 2 and 4 in the above scheme; but when acetylcholine is injected into the body it acts directly on autonomic end-organs, ganglia and skeletal muscle. It was pointed out under the his-

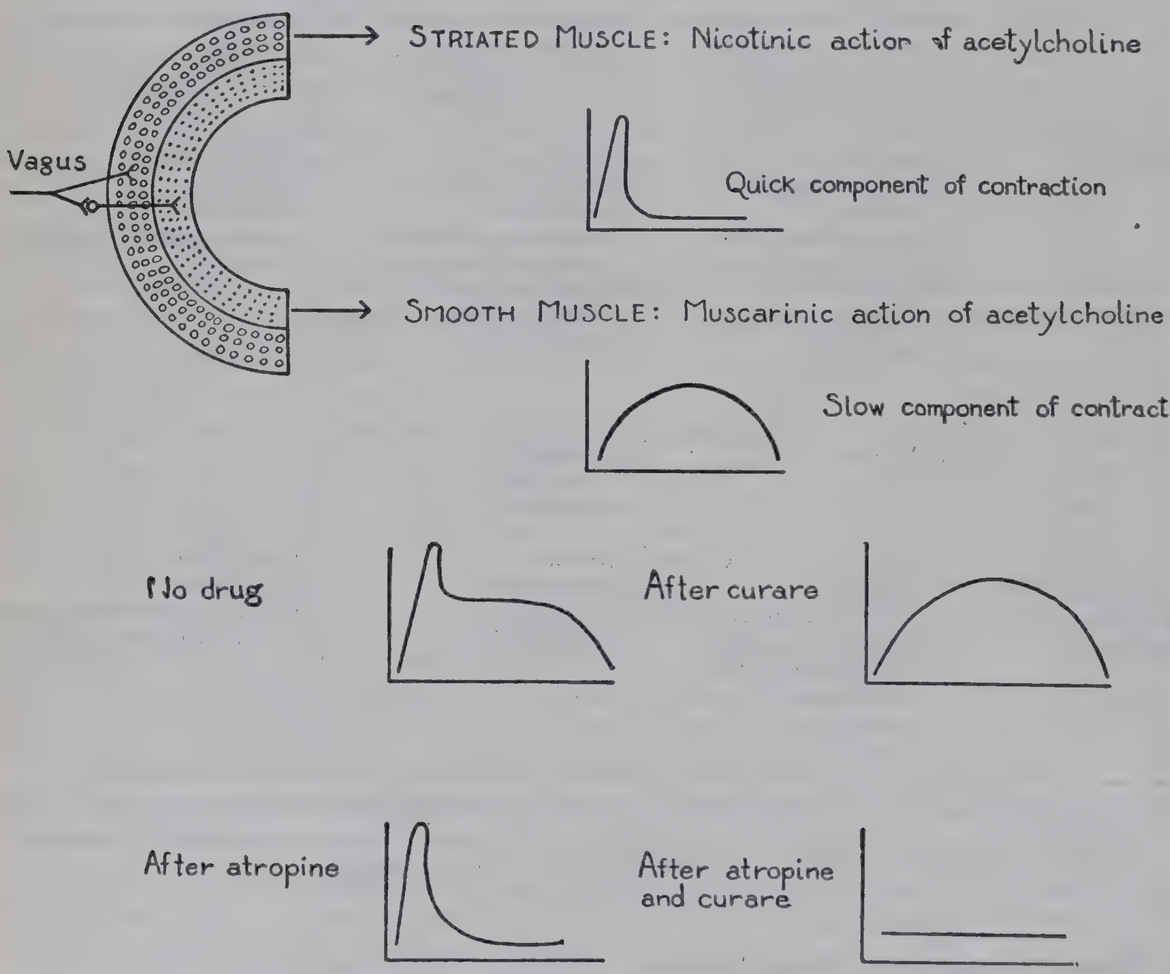
STRIATED MUSCLE: Nicotinic action of acetylcholine
Vagus
Quick component of contraction
SMOOTH MUSCLE: Muscarinic action of acetylcholine
Slow component of contraction
No drug
After curare
After atropine
After atropine and curare

FIGURE 32. *Schematic representation of the nicotinic and muscarinic actions of acetylcholine on striated and smooth muscle, respectively, and the effects of drugs upon these responses. See* text for explanation.

tory of the chemical transmission theory that Dixon noted the fidelity with which the actions of the alkaloid muscarine simulated the effects of parasympathetic nerve stimulation. The similarity in action between acetylcholine and muscarine on autonomic effector organs (smooth muscles and glands) has given rise to the term "*muscarinic*" actions of acetylcholine to distinguish them from the effects on ganglia. For many years it was known that the alkaloid nicotine stimulated autonomic ganglia before paralyzing them. Acetylcholine also possesses the ability to stimulate ganglion cells in low concentrations and to depress them in high concentrations. Furthermore, both nicotine and acetylcholine have similar effects on skeletal muscles. For these reasons the stimulating actions of acetylcholine on ganglia and on voluntary muscles have been termed "*nicotinic*." The nicotinic and muscarinic actions of acetylcholine contrast not only in regard to the effector organs involved, but also in respect to the drugs which block these actions. Nicotine and curare block only nicotinic actions of acetylcholine, nicotine acting especially on ganglia and curare on striate muscle. Atropine prevents only the muscarinic actions. These points can be more readily appreciated by consulting the classification of drugs given in Table 18.

The nicotinic and muscarinic actions of acetylcholine can be strikingly demonstrated on the intestinal tract of a primitive fish known as the tench. This fish has an intestine composed of two muscular coats, the outer one being striated and the inner one smooth. Both types of muscle, however, are supplied by the vagus nerve, and therefore receive cholinergic innervation. The outer muscle coat responds to stimulation with a rapid contraction characteristic of skeletal muscle, and the inner layer responds with a slow contraction characteristic of smooth muscle (Frey, 1928). These facts are *schematically* presented in Figure 32. When the vagus is stimulated, the released acetylcholine excites both components of contraction and these are fused as diagramed in the figure. After *curare,* vagal stimulation yields only the smooth muscle or muscarinic component of contraction because the skeletal muscle is paralyzed. If *atropine* is applied and the vagus again stimulated, only the nicotinic or quick component of contraction is elicited, because atropine blocks the response of smooth muscle to acetylcholine. When *both curare and atropine* are given and the vagus is stimulated, no contraction occurs because both the nicotinic and muscarinic actions of acetylcholine are blocked.

Other *esters of choline,* such as *acetyl-betamethyl-choline* (mecholyl) and *carbaminoylcholine* (doryl) have been introduced into therapeutics in an attempt to obtain drugs which are not so readily susceptible to destruction by cholinesterase and therefore less evanescent in action, which have fewer nicotinic properties and more potent muscarinic effects, and which can be given orally. These drugs presumably act in a manner analogous to acetylcholine, but tend to show selective actions on particular effector cells.

Other Parasympathomimetic Alkaloids. The highly selective action of *pilocarpine* on structures innervated by postganglionic cholinergic nerves and its consequent simulation of the muscarinic and not the nicotinic effects of acetylcholine have never been satisfactorily explained. The same holds true for the alkaloids *muscarine* and *arecoline.* These three drugs are chemically distinct from acetylcholine, do not inhibit cholinesterase as does physostigmine, and act directly on effector cells. Muscular and glandular responses to these chemicals occur after complete nerve degeneration.

Physostigmine (*Eserine*) *and Prostigmine.* These drugs do not act on effector organs, and produce cell responses only by virtue of their ability temporarily to inhibit cholinesterase from destroying acetylcholine produced at cholinergic nerve endings. Thus they exert their effects indirectly in the same location as does acetylcholine, namely at steps 2 and 4.

Epinephrine and Sympathomimetic Drugs. The relation of epinephrine to the chemical mediation of adrenergic nerve impulses has already been discussed.

When epinephrine is injected into the body, it acts directly on smooth muscle and gland cells.

Sympathomimetic drugs such as *tyramine, ephedrine* and *benzedrine* are closely related chemically to epinephrine and presumably act directly on cells innervated by adrenergic nerves (page 424). They differ from the hormone mainly in that ergotoxine fails to reverse their excitatory actions and cocaine does not potentiate their effects.

Cocaine possesses certain sympathomimetic properties and is capable of potentiating adrenergic nerve stimulation and the action of epinephrine. The mechanism is not understood. It is not clear whether cocaine protects epinephrine and sympathin from oxidative destruction or whether it increases membrane permeability so that these substances may more readily diffuse into the reacting cells.

Atropine. Atropine has no effect on the nicotinic actions of acetylcholine but it specifically blocks all the muscarinic actions. Furthermore, it blocks muscarinic responses whether they are excitatory as in the intestine, or inhibitory as in the heart. Atropine prevents completely all the muscarinic responses to injected acetylcholine but is less effective in blocking certain effects of nerve stimulation. Although small doses of atropine prevent cardiac slowing or salivary secretion from occurring after nerve stimulation, large doses will not check the muscular responses of the intestine and the urinary bladder to nerve impulses. One can reasonably inquire why atropine fails to block the responses to certain nerve impulses if the latter act through the release of acetylcholine. The explanation lies in the fact that atropine probably causes a block between steps 4 and 5, that is, it prevents the mediator from penetrating the cell and reaching the receptive substance. When acetylcholine is released by cholinergic nerves, it is probably liberated inside the cell, and atropine evidently cannot prevent the intracellular action of acetylcholine. Histological evidence for this intracellular locus of release of acetylcholine is found in the fact that many autonomic nerve fibers end within the substance of the cell protoplasm. Unfortunately, our knowledge is not sufficiently complete to explain why atropine blocks the effects of certain cholinergic nerve impulses and not those of others. When atropine blocks the effects of nerve stimulation, it does not interfere in the least with the release of acetylcholine at cholinergic nerve endings. It only prevents acetylcholine from entering effector cells.

Ergotoxine and Ergotamine. Ergotoxine and ergotamine specifically block the effects of stimulation of adrenergic nerves. They prevent only excitatory responses to epinephrine or nerve stimulation, whereas atropine checks both excitatory and inhibitory responses. Furthermore, ergotoxine and ergotamine prevent all excitatory responses to adrenergic nerves in contrast to atropine which fails to block certain reactions to nerve stimulation. The ergot alkaloids do not prevent the release of the chemical mediator at adrenergic endings or the formation of sympathin E and I. They therefore do not interfere with the union of the mediator and the receptive substance. Consequently, ergotoxine and ergotamine must block autonomic responses by acting more distally than does atropine. Ergotoxine and ergotamine exert their effects between steps 5 and 6, that is, they block the contractile or secretory mechanism directly.

933F (Fourneau). This synthetic chemical, piperidinomethylbenzodioxan, is of considerable experimental interest because its sympatholytic action is analogous to the parasympatholytic property of atropine. It prevents injected epinephrine from producing responses but it does not effectively check the reactions to stimulation of adrenergic nerves. In this latter respect it differs from ergotoxine. The locus of action of 933F is the same as that for atropine, between steps 4 and 5.

This compound also blocks autonomic ganglia, thus acting between steps 2 and 3, a property not manifested by atropine or ergotoxine.

Curare and Nicotine. These two agents block the effects of the nerve impulse between steps 2 and 3. They block synaptic transmission through autonomic ganglia by acting directly on ganglion cells to render them unresponsive to injected acetylcholine or to acetylcholine released by preganglionic nerve impulses. That the ganglion cells are not paralyzed, however, is shown by the fact that they still respond when stimulated by potassium salts. Ganglionic paralysis by nicotine is preceded by a preliminary phase of stimulation, but this is not noted with curare.

Curare and nicotine also block the neuromuscular junctions in voluntary muscle. The pharmacological similarity between these junctions and autonomic ganglionic synapses will be pointed out. The action of curare and nicotine on skeletal muscle is such that the responses to both acetylcholine and nerve impulses are prevented. Nicotine and curare do not interfere with the release of acetylcholine when somatic motor nerves are stimulated. They therefore act by blocking skeletal muscle cells directly.

Autonomic Blocking Agents Do Not Interfere with the Release of Chemical Mediators. It is well to reemphasize that, although autonomic blocking agents interrupt the sequence of orderly events by which nerve impulses cause effector responses, in no instance do they prevent those impulses from releasing acetylcholine or sympathin. This fact has been repeatedly proved for all types of effector cells. Thus the locus of action of the autonomic blocking agents is always peripheral to the site of release of chemical mediators at nerve endings.

Drugs Having Minor Autonomic Actions. A number of chemical agents have partial or indirect autonomic actions. These include yohimbine, apocodeine, guanidine, strychnine, xanthines and the barbiturates. In the last analysis, the effector cells have distinct chemical properties, and it is not surprising that among the vast number of organic chemicals there exist a few substances which can more or less specifically stimulate or depress certain autonomic cell functions.

Potassium Ions. The ions of potassium occupy a peculiar pharmacological rôle due to their ability to stimulate structures innervated by cholinergic nerves. The neuromimetism of potassium ions is not yet fully understood, nor is it known what part these ions normally play in the physiology of the visceral nervous system. It does not appear, however, that potassium occupies a significant place in the mechanism of action of autonomic drugs. The actions of potassium ions in this respect are more fully discussed on page 596.

Skeletal Muscle Neuropharmacology. The possible rôle of acetylcholine in the mediation of somatic nerve impulses to skeletal muscle has clarified several puzzling phenomena for which pharmacologists previously had no adequate explanation. Although physostigmine and pilocarpine have many actions in common, the former drug causes definite skeletal muscle twitchings not produced by the latter. Nicotine, which is viewed as a drug primarily acting to paralyze autonomic ganglia, is also capable of paralyzing voluntary muscle. Why these drugs act on skeletal muscle when the bulk of anatomical evidence shows that the latter receives no autonomic innervation remains a dilemna which can best be resolved by the theory that somatic motor nerves function through the acetylcholine mechanism. Physostigmine thus affects skeletal muscle by preserving the locally produced acetylcholine from destruction by cholinesterase. The failure of physostigmine to act on skeletal muscle after its nerves are cut and degenerated adds support to this theory, because the drug acts only to preserve acetylcholine and when the latter is not present (as after nerve degeneration) physostigmine has no effect.

Acetylcholine causes both striped and smooth muscles to contract. This is true despite the definite anatomical and physiological differences between these muscles. Although a sharp distinction exists between smooth and skeletal muscle, many similarities can be noted between the skeletal muscle and the postganglionic nerve fiber. Elliot suggested many years ago that the conducted disturbance in skeletal muscle is the physiological equivalent of the postganglionic nerve impulse. There are reasons today to believe this suggestion may be true (Rosenblueth, 1936). If it is correct, then the neuromuscular junctions (motor-end plates) become analogous to the synapses in autonomic ganglia. The cholinergic nerve to a skeletal muscle fiber and that to a ganglion cell are both medullated, and both come directly from cells lying inside the central nervous system. Again, a single spinal motor nerve fiber may supply 100 or more skeletal muscle cells, and the preganglionic autonomic nerve fiber may synapse with a score or more of ganglion cells. Furthermore, the reactions of ganglion cells and skeletal muscle cells to drugs are quite similar, as is indicated in the classification of drugs in Table 18. Both structures are stimulated by acetylcholine and physostigmine, unaffected by pilocarpine and atropine, and functionally severed from the central nervous system by nicotine and curare.

As far as it is now understood, the pharmacology of the autonomic synapse is similar in all major respects to that of the junction between the spinal motor nerve and skeletal muscle. Both structures are relay sites between two waves of impulse conduction, and acetylcholine is apparently a major factor in the transmission of the excitatory state.

Clinical Applications. The concept of transmission of nerve impulses to skeletal muscle by acetylcholine has opened a new field of therapy for certain myopathic disorders. In the case of myasthenia gravis, at least, the mechanism of action of drugs effective against the profound muscular weakness characterizing this disease can be correlated with the chemical mediation of somatic motor nerve impulses. The pathological physiology of myasthenia gravis may be due to: (1) a deficiency in the amount of acetylcholine produced at motor nerve endings, (2) an increase in muscle cholinesterase, or (3) the existence of some abnormal substance or metabolite with a curare-like action which elevates the threshold of skeletal muscle to the effects of nerve impulses. Which of these factors is involved is not known. Nevertheless, physostigmine, prostigmine and certain choline esters give striking relief and return muscular strength to normal. Regardless of the exact etiology of the disorder, the action of these drugs tends to increase the effective concentration of acetylcholine at neuromuscular junctions.

Myotonia congenita is in pharmacological contrast to myasthenia gravis. Theoretically, at least, the symptoms of this syndrome could be explained on the basis of an excess of acetylcholine, and this in turn could be due to the reverse of any of the three factors listed in the preceding paragraph, although it is more likely that the muscle fibers are abnormally sensitive to acetylcholine. Drugs effective in myasthenia gravis aggravate the symptoms of myotonia congenita. In *familial periodic paralysis,* choline esters and potassium salts have given relief.

These examples are given not to present fully solved problems but rather to indicate the many therapeutic ramifications of this field and to show that clinical fruit is ripening on what may have appeared to be a purely academic tree.

Sensitization to Drugs by Nerve Degeneration. For many years it has been known that certain effector structures become more sensitive to drugs when deprived of their nerve supply. Several interesting facts, some of them with direct clinical applicability, have evolved from a reexamination of sensitization in relation to the chemical mediation theory. When postganglionic nerves are cut and degenerate, effector organs become more responsive to chemical mediators. An example of this is seen in the "paradoxical pupillary reaction" (Langendorf, 1900). This reaction consists in the wide dilatation of the sympathetically denervated pupil under certain conditions of sympatho-adrenal discharge. It was first described by Budge (1855) but it was not fully appreciated until many years later (Elliot, 1905, 1912) that sympathetically denervated structures are excessively stimulated by epinephrine.

The phenomenon of sensitization is clearly seen in the smooth muscle of blood vessels in animals and man (*see* Freeman, Smithwick and White, 1934; Ascroft, 1937), and it has significance for the type of neurectomy performed for peripheral vascular disturbances. The following oft-quoted case provides an instructive example. A surgeon performed a cervicodorsal sympathetic ganglionectomy on a woman for Raynaud's disease and the immediate results were apparently quite good. Several days later, he demonstrated the patient to a group of medical students and noted to his surprise that when he pulled back the bedclothes the hands were cold and blanched. A few hours later he revisited the patient alone and the hands were warm and pink. The explanation is that the blood vessels in the denervated area were sensitized to epinephrine and sympathin released by the excitement occasioned by the visit of the medical students. This resulted in marked vasoconstriction in the upper extremities. No such sympatho-adrenal discharge occurred when the doctor visited the patient alone.

It is now clear why for many years better results were obtained by sympathectomies performed for the legs than was the case for the arms. The classical operation for the upper extremity was in reality a postganglionic sympathectomy. In the lower extremity, the lumbar sympathectomy which was performed left intact the postganglionic fibers and thus it was really a preganglionic resection. The latter does not cause degeneration of the nerves to vessels which are therefore not sensitized. It does, however, interrupt the connection of the peripheral effector organs with the central nervous system and cuts off noxious nerve impulses. The Smithwick (1936) preganglionic sympathectomy for the upper extremity is said to yield better results in peripheral vascular diseases than does sympathetic ganglionectomy (postganglionic resection). Not all neurosurgeons, however, agree with this point of view (*see* Fatherree, Adson and Allen, 1940).

Not only does section of excitatory adrenergic nerves result in sensitization of the denervated smooth muscles but resection of inhibitory adrenergic nerves also causes increased sensitivity of the denervated effector organs. Thus, Luco (1937) demonstrated an increased responsiveness of the denervated rabbit intestine and non-pregnant cat uterus to epinephrine, both structures being relaxed by the drug. Similarly, Youmans (1938) showed that the sympathetically denervated dog's intestine was three times more sensitive to the inhibitory effect of epinephrine than was the normal bowel.

Structures innervated by cholinergic nerves are also sensitized to chemicals by interruption of their nerve supply. For example, after excision of the ciliary ganglion, Shen and Cannon (1936) noted an enhanced response of the paralyzed sphincter muscle of the iris to acetylcholine.

Gland cells as well as smooth muscle cells show increased responsiveness to the chemical mediators when their autonomic innervation is interrupted. This has been demonstrated in the lacrimal and submaxillary glands (Maes, 1938; Simeone and Maes, 1939).

Autonomic ganglion cells manifest an increased sensitiveness to acetylcholine and certain other chemicals when they are deprived by section of their preganglionic innervation. Thus, when the preganglionic fibers to an autonomic ganglion are cut, the ganglion cells remain intact but quickly become abnormally sensitive to acetylcholine. It can be shown experimentally, for example, that preganglionic nerve section causes a four-fold increase in the responsiveness of ganglion cells (superior cervical) to acetylcholine (Rosenblueth and Cannon, 1939). Acetylcholine, however, normally does not escape into the circulation from its sites of release due to effective hydrolysis by cholinesterase. Fortunately, for this reason ganglionic sensitization in patients subjected to preganglionic neurectomy is not likely to have adverse clinical reverberations.

Not only are smooth muscles, gland cells and ganglion cells sensitized by nerve degeneration, but skeletal muscles are also sensitized to acetylcholine by degeneration of their motor nerves. In 1863, Philipeaux and Vulpian noted that when the hypoglossal nerve to a dog's tongue was cut, the tongue muscles could be made to contract slowly by stimulation of the sensory lingual nerve. Rogowicz (1885) noted a similar phenomenon in the facial muscles, and Sherrington (1894) in the muscles of the hind leg. Many erroneous explanations were advanced from time to time but it is now known that these slow contractures are caused by acetylcholine leaking onto the denervated sensitized skeletal muscles. The acetylcholine is probably produced locally by the cholinergic vasodilator fibers supplying the blood vessels of the skeletal muscles and these nerve fibers are not interrupted by cutting the spinal motor nerves. The degree of increased sensitivity to acetylcholine of denervated skeletal muscles in mammals has been estimated to be as great as a thousand-fold (Brown, Dale and Feldberg, 1936).

Finally, it has been demonstrated that nerve cells of the central nervous system become sensitized when they are "denervated," *i.e,* deprived wholly or in part of their normal nerve connections. Thus, Haimovici and Cannon (*see* Cannon, 1939), employing the technic of semisecting the lower portion of the spinal cord in animals and testing the responses of the two quadriceps muscles, found that acetylcholine stimulated the denervated cells of the spinal cord in doses which did not affect the intact cells, as judged by the muscular responses obtained. Likewise, the action of strychnine on the spinal cord caused many more muscle contractions on the cut than on the control side, a fact of interest in view of the possible anticholinesterase property of this drug (page 258). The demonstration that spinal neurones respond to partial denervation by an increased sensitiveness to chemicals is in keeping with the theory that chemical mediators may be concerned with central synaptic transmission.

Mechanism of Sensitization by Denervation. The mechanism of sensitization of denervated structures is not understood. Nor is it clear why maximal sensitization requires 14 to 16 days to develop in smooth muscles supplied by adrenergic nerves (Hampel, 1935) but only a few to 24 hours in the case of smooth muscles receiving cholinergic nerves. Muscles become endowed with a specific responsiveness to chemical mediators as a result of the establishment of nerve connections. Armstrong (1935) showed that the growth of vagal fibers into the embryonic myocardium of the fundulus causes the heart to become very sensitive to acetylcholine. After nerve degeneration, this sensitivity of effector organs to chemical mediators and certain drugs evidently becomes greatly enhanced. The extent of this increased responsiveness can be appreciated from the fact that the totally denervated heart responds with acceleration of rate to one part of epinephrine in 1,400,000,000. Regeneration of the nerve supply of a denervated organ results in a gradual loss of the abnormal sensitiveness (Simeone, 1937).

Several possibilities exist to explain the sensitization of effector cells evoked by denervation, including decreased ability to destroy the chemical mediator, altered physical properties in contractile cells, increased amount of stored precursor of the chemical mediator, and enhanced permeability of effector cells. The most plausible explanation is that the permeability of the membrane of the effector cell is increased when the nerve supply degenerates. Two lines of evidence exist for this interpretation. In the first place, the increased sensitivity is not absolutely specific for acetylcholine and epinephrine, but also exists to a certain extent for other stimulating agents. For example, the denervated nictitating membrane is sensitized not only to epinephrine but also to acetylcholine, pilocarpine, histamine and potassium ions. Denervated skeletal muscle is unusually responsive to nicotine and potassium as well as to acetylcholine (Dale and Gasser, 1926). The same is true of autonomic ganglia. The second point is that denervation in smooth muscle results in a lessened electrical potential accompanying the contraction. This may be the result of a diminished polarization of the cell membrane due to an increase in cell permeability.

Law of Denervation. The observations recorded in the foregoing paragraphs have prompted Cannon to suggest that there exists a law of denervation, which may be stated as follows (Cannon, 1939): "When in a series of efferent neurones a unit is destroyed, an increased irritability to chemical agents develops in the isolated structure or structures, the effect being maximal in the part directly denervated." The pertinent literature and physiological significance of the phenomena of sensitization following denervation have been reviewed by Cannon (1939).

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CHAPTER 20

DRUGS STIMULATING STRUCTURES INNERVATED BY CHOLINERGIC NERVES (PARASYMPATHOMIMETIC DRUGS)

I. CHOLINE ESTERS: ACETYLCHOLINE, ACETYL-BETA-METHYLCHOLINE AND CARBAMINOYLCHOLINE

Autonomic drugs stimulating structures innervated by cholinergic nerves may conveniently be divided into three groups, as follows: (1) the choline esters—*acetylcholine, acetyl-β-methylcholine* and *carbaminoylcholine;* (2) the inhibitors of cholinesterase—*physostigmine* (*eserine*) and *prostigmine;* and (3) the older alkaloids, *pilocarpine, arecoline* and *muscarine*. Collectively, all these drugs are known as parasympathomimetic agents, but the three groups contrast sharply in many respects. Their relation to each other and the effector organs upon which they act are indicated in Table 18.

ACETYLCHOLINE

Acetylcholine is a substance of great interest to physiologists and pharmacologists because it produces responses in effector cells which simulate those obtained from stimulation of cholinergic nerves. Its clinical uses, however, are limited because of its instability and consequent transient effects in the body. Nevertheless, a knowledge of the actions of acetylcholine enables one better to understand the other more useful parasympathomimetic agents.

Historical. Acetylcholine was first synthesized by Baeyer in 1867, but for many years it had only a chemical interest. At the turn of the century, Hunt (1899) noted that adrenal extracts from which epinephrine had been removed caused a fall in blood pressure, and although he identified the presence of choline in the extract, he suggested that some precursor of choline, perhaps an ester, was the vaso-depressor agent. In 1906, Hunt and Taveau showed that acetylcholine was 100,000 times more active than choline in causing a fall in blood pressure. Later (1910, 1911), these same investigators reported on the properties of other choline esters including acetyl-β-methylcholine. Ewins (1914) then identified acetylcholine in certain extracts of ergot and Dale (1914), stimulated by this discovery, examined the pharmacological properties of acetylcholine in considerable detail. Dale noted that the chemical mimicked the effects of stimulation of parasympathetic nerves and introduced the term "parasympathomimetic" to describe its properties. He observed that acetylcholine had an evanescent action and that atropine annulled completely the so-called parasympathetic effects. After atropine, however, acetylcholine manifested new properties, namely, an ability to stimulate all autonomic ganglion cells in a manner similar to nicotine. The distinction between peripheral effects on glands and smooth muscle cells (*muscarinic action*) and those on ganglion cells and skeletal muscles (*nicotinic action*) soon occupied the attention of workers in this field and other esters of choline as well as phosphonium, arsonium, stibonium and sulfonium bases were investigated for their pharmacological properties (Hunt and Renshaw, 1925, *et seq.;* Simonart, 1932; Comroe and Starr, 1933; Molitor, 1936; and others).

Parallel with the foregoing studies came the important discovery of Loewi concerning the rôle of acetylcholine in the chemical mediation of the nerve impulse and the subsequent elaboration of the hypothesis of this substance as the transmitter of the excitatory state across ganglionic synapses and neuromuscular junctions in voluntary muscles. The story of these discoveries and their profound importance for physiology and pharmacology has been presented in detail (Chapter 19).

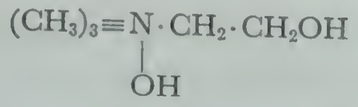
Relationship Between Chemical Structure of Choline Derivatives and Pharmacological Actions. Choline, in common with other quaternary ammonium bases, possesses three distinct types of pharmacological action: muscarinic, nicotinic and curariform. The manifestations and significance of these types of responses and the drugs which antagonize them have been discussed (Chapter 19). Numerous esters, ethers and other derivatives of choline have been studied in an attempt to find the basis for the susceptibility of the compounds to hydrolytic destruction in the body by cholinesterase, the relative prominence of the three types of actions, and the special affinities of the drugs for particular autonomic effector organs. Only certain salient features can be presented; the details may be found in pertinent publications (Hunt and Taveau, 1911; Hunt and Renshaw, 1925, *et seq.;* Simonart, 1931, *et seq.;* von Oettingen and Elveleth, 1932; Molitor, 1936; and others).

Derivatives of choline may exert all, none or varying combinations and intensities of the three basic actions listed. For example, replacing the alcoholic hydroxyl by a carboxyl group (to yield betaine) results in a compound which is practically inert. Methyl and ethyl esters of β-methylcholine cause only muscarinic responses. The ethers of triethylammonium compounds, on the other hand, manifest only curariform effects. Lengthening of the side-chain of choline usually increases its muscarinic potency, whereas shortening the chain increases the nicotinic action. Esterification of the alcoholic hydroxyl of choline also increases the muscarinic action. Esters of choline are rapidly hydrolyzed by the blood and tissues whereas ethers of choline are unaffected by cholinesterase. Also, the esters are far more effective in liberating epinephrine from the adrenal medulla than are the ethers (Simonart, 1932).

In regard to the clinically useful compounds, acetylcholine resembles choline itself except that it is from 500 to 100,000 times more potent, dependent on the particular response which is being observed. Acetyl-β-methylcholine resembles acetylcholine except that it lacks the marked stimulating action on autonomic ganglia. Carbaminoylcholine, on the other hand, has a greater nicotinic effect than acetylcholine. The ethyl ether of β-methylcholine resembles acetyl-β-methylcholine except that it is much more stable. In addition, this compound serves to illustrate the occasional affinity of these drugs for specific effector organs. The ether derivative causes marked miosis upon systemic administration to cats whereas this response is not seen either after esters of β-methylcholine or lethal doses of the ethyl ether of choline (Simonart, 1932). Optical activity also influences the pharmacological behavior of the choline derivatives. For example, the levorotatory acetyl-β-methylcholine exerts a much smaller muscarinic effect than the dextrorotatory isomer, but only the latter is hydrolyzed by the cholinesterase of cat or rabbit serum. Yet neither isomer exerts any action on autonomic ganglia and both are active on denervated skeletal muscle (Simonart, 1938). Certain salient features of the choline compounds employed in therapeutics are shown in Table 19.

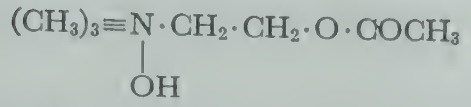
Chemistry, Preparations, Doses and Administration. The structural formula of acetylcholine and its relationship to choline and to other choline esters are as follows:

Choline



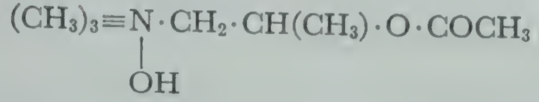
$(CH_3)_3{\equiv}\underset{\displaystyle OH}{\underset{|}{N}}{\cdot}CH_2{\cdot}CH_2OH$

Acetylcholine



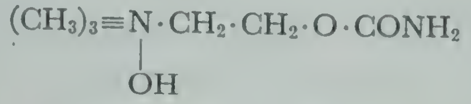
$(CH_3)_3{\equiv}\underset{\displaystyle OH}{\underset{|}{N}}{\cdot}CH_2{\cdot}CH_2{\cdot}O{\cdot}COCH_3$

Acetyl-β-methylcholine



$(CH_3)_3{\equiv}\underset{\displaystyle OH}{\underset{|}{N}}{\cdot}CH_2{\cdot}CH(CH_3){\cdot}O{\cdot}COCH_3$

Carbaminoylcholine



$(CH_3)_3{\equiv}\underset{\displaystyle OH}{\underset{|}{N}}{\cdot}CH_2{\cdot}CH_2{\cdot}O{\cdot}CONH_2$

Acetylcholine is also closely allied to muscarine. The drug is not official and is not described in N.N.R. It is available, however, in the form of the chloride and bromide salts. *Acetylcholine Chloride* and *Acetylcholine Bromide* are white, odorless, hygroscopic, crystalline powders. Both salts are very soluble in water and alcohol and are easily decomposed by heat and alkali. They should be kept tightly stoppered. Sterile ampules containing measured amounts of the dry salts are available for preparing aqueous solutions for parenteral injection.

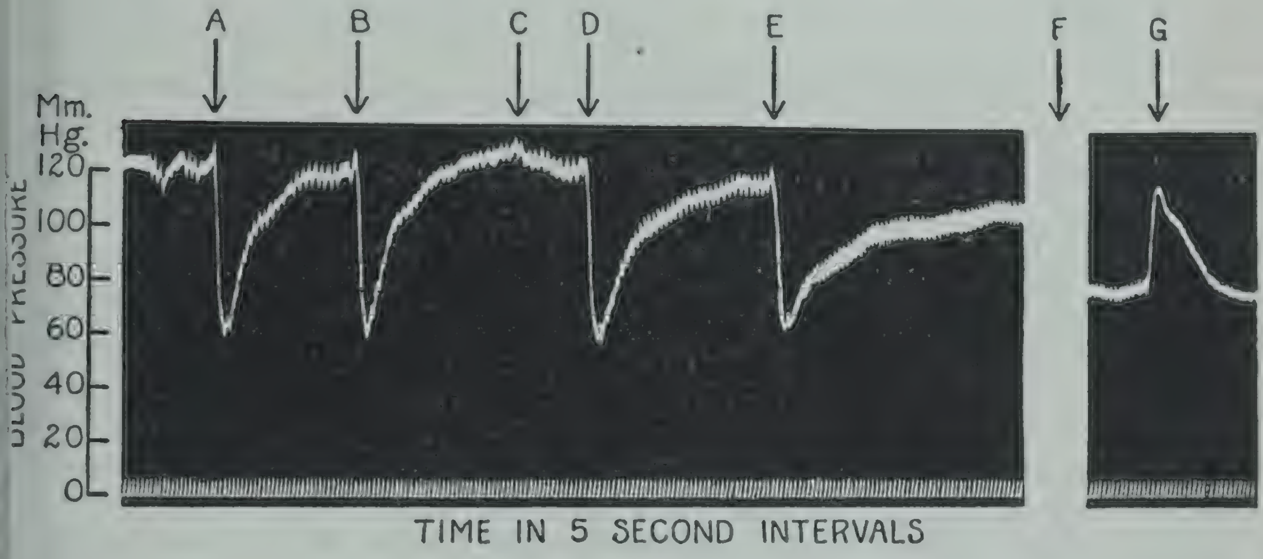


FIGURE 33. *General autonomic pharmacology: the effect of serum cholinesterase on acetylcho- ne and carbaminoylcholine, and the demonstration of the stimulant (nicotinic) action of cetylcholine on autonomic ganglia.*

A. Intravenous injection of 10 micrograms of acetylcholine in a cat under pentobarbital nesthesia causes a typical vasodepressor response. *B.* Injection of 10 micrograms of acetylcholine, cubated for one one hour with dog serum plus a minute amount of eserine, manifests the aracteristic vasodepressor action. The eserine prevented the dog serum cholinesterase from estroying the acetylcholine. *C.* Injection of 10 micrograms of acetylcholine, similarly incubated r one hour with dog serum but without the addition of eserine, fails to elicit a fall in blood ressure due to destruction of the drug by cholinesterase. *D.* Injection of 10 micrograms of carminoylcholine causes an equal fall in blood pressure. Observe the longer duration of action e to slower destruction of this compound in the body. *E.* Injection of 10 micrograms of carminoylcholine, incubated for one hour with the same amount of dog serum as in *C* above, ntinues to elicit a fall in blood pressure without a decrement, indicating that this choline rivative is quite stable and resistant to hydrolytic destruction by cholinesterase. *F.* Interval of minutes during which the test cat was atropinized and eserinized. *G.* Injection of 500 microms of acetylcholine: note the rise in blood pressure resembling that produced by a small dose of inephrine and caused by the nicotinic effect of acetylcholine, that is, a sympatho-adrenal disarge. Atropine prevents the vasodepressor muscarinic response, and eserine protects the etylcholine from destruction in the body. For further details, see text.

The *dose* depends upon the results desired. The drug is practically inert when taken by mouth due to its hydrolytic destruction by gastro-intestinal enzymes and consequently it must be given intramuscularly, subcutaneously or by iontophoresis. The dose by injection varies from 40 to 200 mgm.

Mechanism of Action. Acetylcholine apparently acts directly upon effector cells to elicit their characteristic responses. Whether this action concerns the receptive substance or the reactive material of the cell is unknown. The mechanism of action of acetylcholine is more fully elaborated elsewhere (page 338). Cells reacting to the drug fall into two distinct categories, those cells innervated by (1) postganglionic cholinergic nerves (*i.e.,* smooth muscle and gland cells) and (2) preganglionic nerves and somatic motor nerves (*i.e.,* autonomic ganglion cells and skeletal muscle fibers). The actions of the drug on these two groups of effector cells have been termed the *muscarinic* and *nicotinic* actions, respectively. The details and significance of these two types of response are given on page 339. Atropine blocks only muscarinic actions of acetylcholine; nicotine (in large doses) and curare, only nicotinic actions (pages 340, 341) (Table 18).

The responses to acetylcholine in the body are further characterized by their transient and evanescent nature (Figure 33). This is due mainly to the fact that acetylcholine is hydrolyzed to acetic acid and the pharmacologically impotent choline by *cholinesterase,* an enzyme present in blood and tissues. The properties, distribution and physiological importance of this enzyme are fully presented in the introductory chapter to the autonomic drugs. Eserine and prostigmine prolong and intensify the responses to injected acetylcholine by inhibiting cholinesterase.

Pharmacological Properties

By reference to the responses of effector organs to cholinergic nerve impulses, as listed in Table 17, one can predict accurately the effects of the administration of acetylcholine. Certain responses, however, are not detectable unless special technics are used to elicit them. Thus, the rise in blood pressure due to the nicotinic action of acetylcholine on the sympathetic ganglion cells and on the adrenal medulla does not become manifest unless the fall in blood pressure, due to the muscarinic action of the drug on smooth muscle cells of blood vessels, is prevented by atropinization. This is due to the fact that the muscarinic responses to acetylcholine normally predominate. In this connection, it may be stated that the evanescent character of the responses to acetylcholine is due not only to the hydrolytic destruction of the ester by cholinesterase, but also to the fact that the nicotinic actions of the drug are in opposition to the muscarinic. The acetylcholine-induced sympatho-adrenal discharge tends to counteract many of the peripheral autonomic effects of the drug, as is evident from an inspection of Table 17. The major characteristics of acetylcholine in comparison with allied choline derivatives are shown in Table 19.

Cardiovascular Action. Typical cardiovascular responses to acetylcholine can only be seen when a sufficiently large dose is given to an experimental animal. The drug then causes vasodilatation, especially of smaller blood vessels, a fall in blood pressure, various grades of heart block from partial to complete auriculoventricular dissociation, and cardiac slowing which may proceed to complete asystole.

Various arrhythmias and electrocardiographic abnormalities can be produced in experimental animals by intravenous injection of acetylcholine (Goldenberg and Rothberger, 1934; Noth, Essex and Barnes, 1939). These include a decrease in the height, notching and diphasic character of the P wave, partial and complete heart block, ventricular standstill of varying duration, and auricular fibrillation and auricular tachycardia. The drug appears to cause only slight depression of the sino-auricular node and more marked depression of the auricular musculature, the auriculoventricular node and the bundle of His. These actions are favorable for abolishing paroxysmal tachycardia of auricular or A-V nodal origin. Starr (1936) has reported the interesting fact that quinidine diminishes or abolishes the ability of acetylcholine to slow the cardiac rate in intact anesthetized animals or in isolated hearts. This action of the alkaloid is not identical with that which blocks the response of the heart to vagal stimulation. Patients with paroxysmal tachycardia may thus not respond to therapy with choline esters if they are receiving quinidine.

TABLE 19

COMPARATIVE CHEMICAL, PHYSIOLOGICAL AND PHARMACOLOGICAL PROPERTIES OF ACETYLCHOLINE, ACETYL-BETA-METHYLCHOLINE AND CARBAMINOYLCHOLINE

Drug	Chemical Properties		Physiological Properties		L.D.$_{50}$ in Rats in Mgm/Kg			Equally Effective Doses on Rabbit's Blood Pressure in Mgm/Kg			Minimum Effective Cathartic Dose in Dogs in Mgm/Kg	
	Stability in Air	Stability in Water	Susceptibility to Cholinesterase	Nicotinic Action	Intravenous	Subcutaneous	Oral	Intravenous	Subcutaneous	Oral	Subcutaneous	Oral
Acetylcholine	Hygroscopic	Unstable	++	+	22	250	2500	0.002	1.0	1000	0.8	40
Acetyl-β-methylcholine	Hygroscopic	Unstable	+	−	20	75	750	0.002	0.2	50	0.05	25
Carbaminoylcholine	Non-hygroscopic	Stable	−−	++	0.1	4	40	0.002	0.1	2	0.01	0.25

Molitor, 1936.

The effects of acetylcholine on the coronary arteries has been studied by several investigators and the results vary considerably depending on the technic, doses of drug and species employed (Smith and associates, 1926; Wedd and Fenn, 1933; Orzechowski, 1933; Goldenberg and Rothberger, 1934). In cat, dog and rabbit hearts, Wedd (1936) found that acetylcholine caused a prompt increase in coronary outflow which was followed by a decrease. The vasodilator effect was thought to be caused by the muscarinic component of action of the drug; the vasoconstrictor effect, by the nicotinic. Katz and associates (1938) observed that only coronary vasodilatation occurred from acetylcholine in the perfused isolated dog heart, whereas both coronary dilatation and constriction were produced by the drug in isolated cat hearts. All effects of acetylcholine on the coronary arteries of both species were abolished by atropine. The finding that acetylcholine causes only coronary vasodilatation in the dog heart, an organ similar at least experimentally to the human heart, seriously challenges the currently accepted view that cholinergic (vagal) impulses to the coronary arteries produce vasoconstriction, and supports the experimental results of Katz and Jochim (1939) who found in dogs that the only vasoconstrictor fibers to the coronaries are adrenergic in character and run in the sympathetic pathway, and that the vagal fibers are cholinergic vasodilators. No cholinergic vasoconstrictor fibers were found in the vagi (page 405) (Katz and Lindner, 1939).

In man, the use of therapeutic doses of acetylcholine produces little change other than vasodilatation and slight fall in blood pressure. This is due to the rapid destruction of the compound and to the efficient compensatory cardiovascular reflexes mediated through the vasosensitive carotico-aortic receptors. In addition, the sympatho-adrenal discharge produced by the nicotinic action of acetylcholine tends to counteract any marked alterations in the heart and blood vessels. Only when large doses are administered intravenously can responses be elicited similar to those obtainable in anesthetized animals. Ellis and Weiss (1932) studied the cardiovascular responses of healthy men to the intravenous and intra-arterial injection of acetylcholine. They found that continuous intravascular injection of solutions of acetylcholine could be made for prolonged periods of time without symptoms or objective signs and with no evidence of cumulative action. Twenty to 60 mgm per minute had to be infused in order to obtain minimal effects. The maximum tolerated dose producing toxic symptoms was 90 to 140 mgm per minute. As much as one gram was injected over a period of 10 minutes. Thus man can destroy the drug rapidly and can therefore tolerate extremely large amounts. This is in sharp contrast to his sensitivity to acetyl-β-methylcholine, which Weiss and Ellis (1934) have shown can be tolerated intravenously only in doses 1/200 that of acetylcholine (Figure 34).

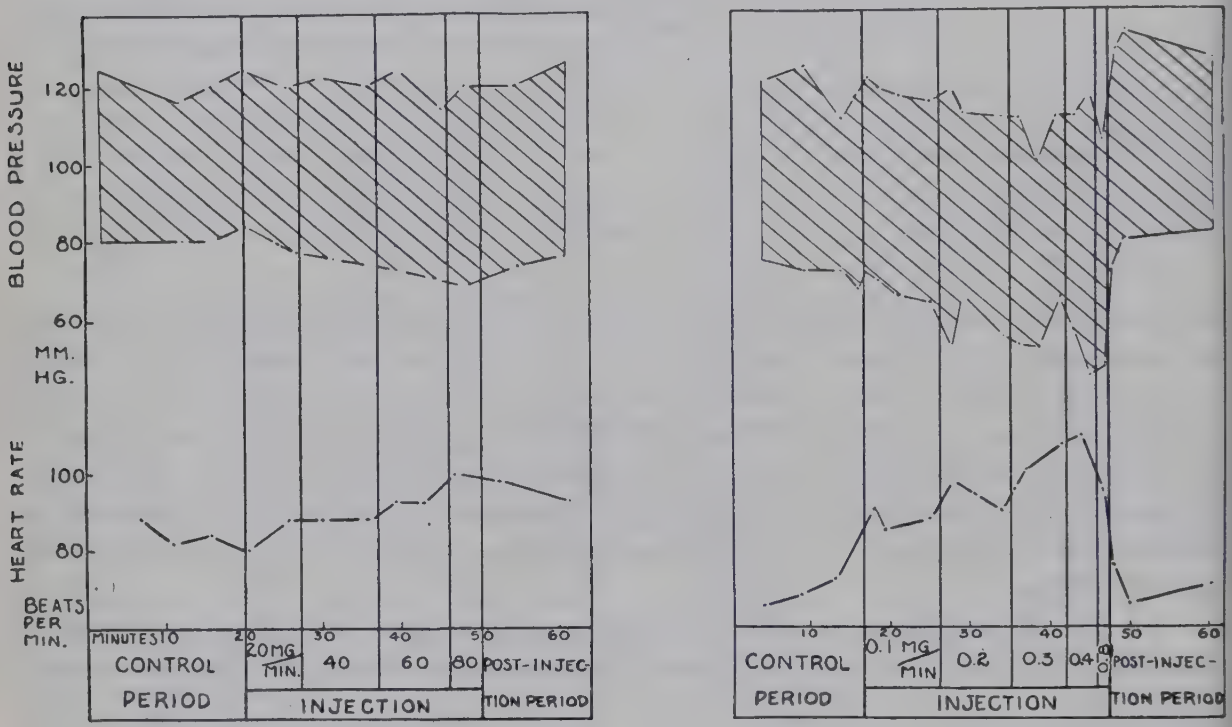


FIGURE 34. *The comparative effect of increasing rates of intravenous infusion of acetylcholine and acetyl-β-methylcholine on the arterial blood pressure and on the heart rate in a normal adult.*

Because acetyl-β-methylcholine is less rapidly inactivated in the body by cholinesterase, it is approximately 200 times more potent than acetylcholine in evoking cardiovascular responses in man. Whereas the intravenous infusion of acetylcholine at the rate of 20 mgm per minute produces minimal effects and 80 mgm produces marked effects, it requires only 0.1 mgm of acetyl-β-methylcholine per minute to evoke minimal and 0.4 mgm marked responses. Both compounds can be infused at a rate producing definite symptoms for prolonged periods without evidence of cumulative action. For a description of the symptoms and signs observed, see text. (After Weiss and Ellis, 1934. Courtesy of the *Journal of Pharmacology and Experimental Therapeutics.*)

Symptoms and signs observed during acetylcholine administration were directly proportional in intensity to the size of the dose and included flushing of the skin, warmth, increase in skin temperature, throbbing in the head, palpitation, relaxed peripheral arteries and bounding pulse, profuse sweating, salivation and lacrimation, substernal constriction accompanied by inspiratory difficulty and slight cough, and nausea and vomiting when the dose was pushed to the limit of tolerance. Symptoms remained at a given level of intensity as long as the dose was unchanged, and all of them subsided without residual effects within a few minutes after cessation of the injection. Bradycardia was never noted. Indeed, cardiac rate was moderately speeded, obviously a compensatory effect. Systolic and diastolic blood pressures were never lowered significantly by the acetylcholine infusion, and changes in cardiac output were not noted. In a later study, Weiss and Ellis (1934) also demonstrated that acetylcholine caused no increase in circulatory velocity. The injection of acetylcholine into the femoral artery caused regional dilatation of arteries and arterioles as shown by bright flushing, marked sweating, increased skin temperature, and enhanced pulse pressure in the vessels as measured by their oscillometric excursion. A marked local increase in total blood flow was indicated by a fall in the arteriovenous-oxygen difference of the blood in the femoral artery and vein. Systemic effects did not occur from intra-arterial injection of the drug.

Large doses of acetylcholine given orally to patients produce no pharmacological actions. Kovacs and coworkers (1936), however, found that an occasional patient showed typical reactions from the oral ingestion of two grams of the drug. When large doses of acetylcholine (50 to 100 mgm) were injected subcutaneously in human beings, both Starr and coworkers (1933) and Weiss and Ellis (1934) noted practically no systemic effects, and Carmichael and Fraser (1933) injected doses of as much as 500 mgm intramuscularly or subcutaneously without producing alterations in pulse rate or blood pressure. Carmichael and Fraser observed transient bradycardia and fall in blood pressure when 10 to 30 mgm were injected very rapidly intravenously. In other respects, their observations corroborate those of Ellis and Weiss.

Gastro-Intestinal Actions. Although sufficiently large doses of acetylcholine cause increased tone, amplitude of contraction and peristalsis in the stomach and intestine and stimulate gastro-intestinal secretions, practically no effect is noted in man even when doses approaching the limit of tolerance are injected intravenously. Nausea and vomiting were the only symptoms referable to the alimentary canal observed in the experiments of Ellis and Weiss cited. The transient effects of acetylcholine on the intestine of the anesthetized cat may be seen in Figure 45. Wilkinson (1932) found that the effect of acetylcholine on gastric secretion was uncertain and less pronounced than that of histamine.

Glandular Actions. The secretory activity of all gland cells receiving cholinergic innervation is enhanced by the muscarinic action of acetylcholine, an effect quickly and completely abolished by atropine. In man, the salivary, lacrimal and sweat glands are particularly stimulated and the effects produced comprise some of the major objective features of the response to intravenously administered acetylcholine.

Respiratory Actions. Effective doses of acetylcholine cause bronchospasm and increased secretion of the bronchial glands. Heymans and coworkers (1936) describe hyperpnea and tachypnea resulting in dogs from the effect of acetylcholine on the chemosensitive receptors of the carotid sinus. Schweitzer and Wright (1938) have analyzed the effects of acetylcholine on respiration in cats. The drug causes a "triple" response consisting of initial stimulation, subsequent depression and secondary stimulation. It was also found by these investigators that acetylcholine stimulates the chemoreceptors in the carotid sinus and aortic arch. The inhibitory effects appeared due to a direct action of the chemical on the respiratory center and spinal cord. In man, some inspiratory difficulty and cough may result from intravenous injection of large doses. The symptoms are transient, readily blocked by atropine and are unimportant except in patients inclined to have asthmatic attacks.

Miscellaneous Effects. When acetylcholine is injected into the carotid artery, as has been done in man by Battro and Lanari (1937), temporary apnea and homolateral facial vasodilatation and sweating, lacrimation and miosis may be observed. The nicotinic action of acetylcholine in skeletal muscle in man is not observed unless the drug is injected into patients with myasthenia gravis. Under these circumstances, recovery of muscle power is demonstrable (Fraser and coworkers, 1937). Applied locally to the eye, acetylcholine is not miotic unless strong concentrations are used (five per cent solution) accompanied by massage (Molitor, 1936).

Therapeutic Uses

Although acetylcholine has been studied pharmacologically since 1906, no attempt was made to use it or other esters of choline in therapeutics until Villaret and Justin-Besançon (1928, 1929) employed acetylcholine in a wide variety of diseases. It was quickly recognized, however, that the transient and variable effects of acetylcholine make it unsuitable for clinical use, especially when sustained action is desirable, and other choline esters have been substituted for it. Acetylcholine, however, has been employed for a number of diseases, particularly those of blood vessels. Thus it has been tried in *Raynaud's disease, thromboangiitis obliterans, arteriosclerosis obliterans, gangrene, varicose* and *trophic ulcers* and *hypertension*. The drug has also been employed in *scleroderma, arthritis, atonic constipation, paroxysmal tachycardia, lead colic, tobacco amblyopia* and *myasthenia gravis*. In most of these disorders the results obtained have not been encouraging. Kovács and associates (1936) found acetylcholine ineffectual when administered by iontophoresis in the treatment of various peripheral vascular diseases. Abbott (1939), however, has reported successful termination of attacks of *paroxysmal tachycardia* in five patients by the intravenous injection of 100 mgm of acetylcholine. Apparently side-effects were minimal. Likewise, several investigators have reported that hypodermic administration of acetylcholine has produced definite improvement in vision in patients with *tobacco amblyopia* (Orr, 1936; Duggan, 1937; Cragg, 1936). In *myasthenia gravis,* Fraser and coworkers (1937) noted return of muscle power after subcutaneous injection of acetylcholine. Prostigmine, however, is the parasympathomimetic drug of choice.

ACETYL-BETA-METHYLCHOLINE

The unsuitability of acetylcholine for therapeutic purposes stimulated the search for synthetic choline esters which would be more stable in the body and therefore more persistent in their actions. Of more than 200 choline derivatives which have been synthesized and studied, only acetyl-β-methylcholine and carbaminoylcholine are satisfactory for clinical use. Although acetyl-β-methylcholine was studied by Hunt and Taveau as early as 1911, it was not until the systematic investigations of this compound by Simonart (1932) and Starr and associates (1933, *et seq.*) that the drug received adequate therapeutic trial. Major and Cline (1932) first synthesized the compound by a process which makes the drug available in quantity.

A major object of endeavor in the field of synthetic choline esters has been to obtain drugs which would have greater stability and hence more sustained actions in the body. A second objective has been to find derivatives which would be relatively free of nicotinic effects (*i.e.*, actions on sympathetic ganglia and skeletal muscle); but, so far as the clinical use of these compounds is concerned, the second objective is relatively unimportant because the nicotinic actions are not manifested except with large doses under special circumstances. Finally, attempts have been made to find choline esters which would selectively affect certain structures in the body and not others, and hence lend themselves to special fields of usefulness. Whether this goal can be obtained is not yet clear. Clinically, however, the choline esters differ somewhat in the responses they elicit and hence each has been employed for certain fairly definite therapeutic purposes.

Mechanism of Action. Present knowledge indicates that acetyl-β-methylcholine exerts its characteristic effects in the body in a manner similar to that of acetylcholine. The drug is less readily hydrolyzed by cholinesterase than is acetylcholine, and this is the basis for its longer duration of action. Physostigmine and prostigmine, through inhibition of cholinesterase, intensify and prolong the responses to acetyl-β-methylcholine, and atropine quickly and completely abolishes all the muscarinic actions of the drug. The nicotinic properties are less prominent than are those of acetylcholine, and thus it is usually impossible to elicit a rise of blood pressure in an atropinized animal even though large doses of acetyl-β-methylcholine are administered. Responses in skeletal muscle, however, are demonstrable, especially in patients with myasthenia gravis.

Pharmacological Properties

The pharmacological properties of acetyl-β-methylcholine are qualitatively similar to those of acetylcholine, except that the former compound is more stable (Figure 34) and lacks nicotinic effects on autonomic ganglia. Some of the major characteristics of the drug in comparison with allied choline derivatives are shown in Table 19.

Cardiovascular Actions. After adequate doses of acetyl-β-methylcholine, the peripheral vessels dilate, the heart slows and the blood pressure falls. These effects are particularly prominent in anesthetized animals. Small doses of atropine block completely all these cardiovascular responses, but even large doses of the drug do not cause a rise in blood pressure in an atropinized animal similar to that seen after acetylcholine. The bradycardia induced in anesthetized cats and isolated hearts by acetyl-β-methylcholine is blocked by quinidine in a manner similar to that mentioned for acetylcholine, and quinidine also antagonizes the prolongation of auriculoventricular conduction produced by acetyl-β-methylcholine in intact animals (Starr, 1936). Hoff and Nahum (1934) found that the ventricular rhythms produced in cats by epinephrine could be abolished by acetyl-β-methylcholine, and that the ventricular fibrillation following electric shock could be prevented by prior administration of the drug, although auricular fibrillation still appeared (Hoff and Nahum, 1935).

The coronary arteries were found by Wedd (1936) to respond to acetyl-β-methylcholine by primary vasodilatation followed by vasoconstriction, in a manner similar to that noted for acetylcholine, but the latter drug was the more active of the two. In the intact dog, acetyl-β-methylcholine tended to cause a decrease in coronary flow. Katz and associates (1938) noted that the drug caused coronary vasoconstriction in isolated perfused cat hearts but in dog hearts only vasodilatation occurred. The physiological significance of the results obtained by Katz and coworkers in dog hearts with choline esters in regard to the effects of nerve impulses on the caliber of the coronary arteries has been mentioned (page 353). Essex and coworkers (1940), employing trained unanesthetized dogs and the thermostromuhr technic for measuring coronary circulation, found that acetyl-β-methylcholine produced a marked increase in coronary blood flow.

In man, Weiss and Ellis (1934) compared the effects of constant *intravenous* infusion of varying doses of acetylcholine and acetyl-β-methylcholine (Figure 34). The symptoms and signs produced were identical with those described for acetylcholine, but the effective doses were approximately only $\frac{1}{200}$ as large. Thus, a dose of 0.1 mgm per minute caused minimal effects and a dose of 0.4 mgm per minute approached the limit of tolerance. Symptoms disappeared within one minute after the injection was terminated, and there was no evidence of cumulative action. Starr and associates (1933) investigated the effects of acetyl-β-methylcholine given *subcutaneously* and *intramuscularly* to normal subjects. Typical responses observed after a dose of 20 mgm are charted in Figure 35, and it will be noted that a transient fall in blood pressure and a compensatory tachycardia occurred, being less persistent than salivation and sweating. The tachycardia was often replaced by a cardiac rate slower than that present in the control period. Arrhythmias were not encountered. The flush, as a rule, was confined to the emotional blush area. With larger doses, the flush may spread over the chest and trunk (rarely below the umbilicus) and also to the arms and legs. In hypertensive individuals, Page (1935) noted that the flushing as well as sweating did not include the hands and feet. The acute stage of action of the drug lasts only two or three minutes, all the effects vanishing within 15 to 20 minutes.

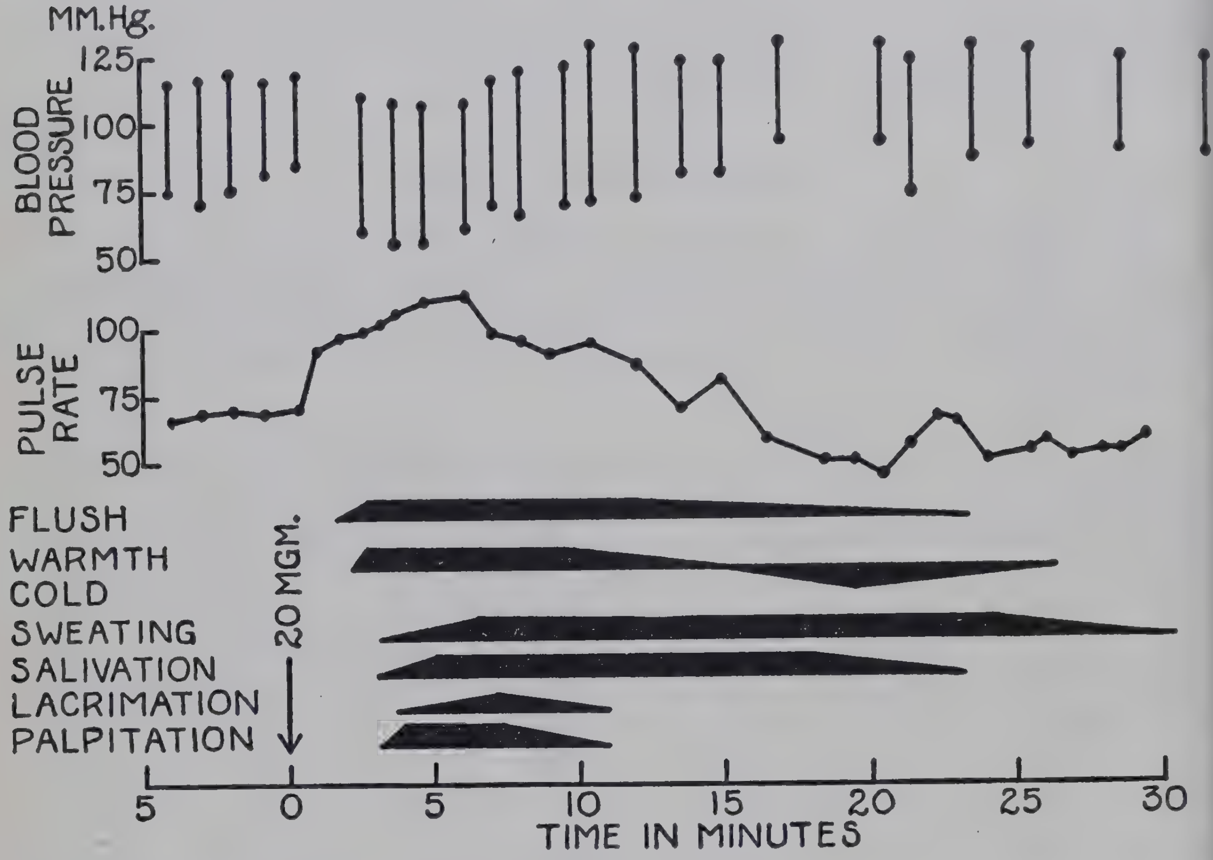


FIGURE 35. *The effect of acetyl-β-methylcholine in man.*

Normal young adult, recumbent posture, 20 mgm of acetyl-β-methylcholine chloride injected subcutaneously at zero time after a preliminary rest period. Note that the first evidence of action of the drug—fall in blood pressure, rise in pulse rate, flushing and a sensation of warmth—appears within one minute. After three minutes, salivation, lacrimation, sweating and palpitation occur and soon reach their maximal intensity. The cardiovascular responses are transient and a bradycardia develops when the blood pressure returns to normal. Chilliness is complained of by subjects who feel warm during the flush. Complete recovery is attained within 15 to 20 minutes after the injection. Additional signs and symptoms are described in the text. Compare this figure with the responses to carbaminoylcholine charted in Figure 37. (After Starr, Elsom, Reisinger and Richards, 1933. Courtesy of the *American Journal of the Medical Sciences.*)

When acetyl-β-methylcholine was administered *orally,* Starr and associates (1933) observed that doses from 50 to 100 times as large as the effective subcutaneous doses had to be employed before noteworthy effects were observed, and these were slow and gradual in onset and mild in character. For example, after a dose of one gram, the blood pressure fell, the diastolic more markedly than the systolic, the pulse rate slowed, the typical flush appeared, and occasionally the skin temperature of the extremities rose, indicating vasodilatation. Arrythmias were not observed and the cardiac output was unaffected.

The ability of acetyl-β-methylcholine to cause *peripheral vasodilatation* and an increase in skin temperature was also studied by Goldsmith (1936), who administered the drug orally to a large group of individuals in doses of from 50 to 1500 mgm. She observed that the skin temperature of the digits often rose six degrees C. or more, vasodilatation being more marked, with a given dose, in the hands than in the feet and greater in patients with vascular spasm than in those with organic occlusion. Those with thromboangiitis obliterans or arteriosclerosis required doses of from 1.0 to 1.5 grams, but patients with vascular spasm sometimes responded to doses of from 50 to 100 mgm. No untoward effects were observed from repeating even the large amounts three times daily, and the changes in blood pressure and pulse rate were insignificant. On the other hand, in hypertensive patients to whom adequate doses of the drug were administered orally or subcutaneously, Page (1935) could detect no increase in skin temperature of the hands and feet despite other evidences that the compound was acting.

In patients with essential or nephritic hypertension, small doses of acetyl-β-methylcholine (2.5 mgm subcutaneously) have been found to cause a moderate to marked decrease in blood pressure whereas the same dose has only a slight effect in normal persons, the percentile fall in pressure averaging three to four times that which occurred in normal controls (Engle and Binger, 1939). Even in those hypertensive patients whose blood pressure had decreased to normal during the control rest period, a greater percentile fall occurred, indicating that the disease itself and not the absolute level of the high blood pressure is the important factor conditioning the decrease in tension noted after the drug. It was also observed that the cold pressor response in hypertensive patients was reduced by the prior administration of acetyl-β-methylcholine. Apparently the peripheral vessels in patients with hypertension respond to the drug with a proportionally greater dilatation than do those of normal persons. Occasionally, the fall may be marked, and Page (1935) records the case of a hypertensive patient whose blood pressure fell from 210/140 to 96/70 after a 20 mgm subcutaneous dose of the compound. Large oral doses (four grams daily) produced either slight and variable reduction or no significant change of the blood pressure of hypertensive subjects. In artificial hypertension induced in human subjects by benzedrine, Loman and coworkers (1939) observed that acetyl-β-methylcholine given by iontophoresis produced a definite fall in blood pressure. In patients with senile hypertension, the choline ester given by the same technic was rarely effective unless preceded by an injection of prostigmine.

The combined administration of acetyl-β-methylcholine and prostigmine may cause *cardiac arrhythmias*. Thus Myerson and associates (1937) observed that the subcutaneous injection of 20 mgm of the choline ester following 0.5 mgm of prostigmine may result in various degrees of severe heart block, and even complete auriculoventricular dissociation. Atropine prevents or abolishes the block. Nahum and Hoff (1935) also observed disorders of cardiac rhythm in patients receiving acetyl-β-methylcholine. In four patients with hyperthyroidism, large doses of the drug (0.75 mgm per kg) produced transient auricular fibrillation. In one patient with auricular flutter and a 2:1 block, acetyl-β-methylcholine induced transient auricular fibrillation with a very slow ventricular rate. Flutter of the auricles did not appear in passing to or from fibrillation. The drug also caused alterations in the ventricular complexes and displacements of the ST segments. The ability of the choline ester to cause a brief period of auricular fibrillation in cats receiving electrical stimulation has been mentioned. Nahum and Hoff believe that auricular fibrillation in these cases is caused by a combination of cholinergic stimulation of the auricle plus an excitant factor, such as thyroxin, electric shock or possibly auricular distention. Page (1935) observed that doses of 10 mgm of acetyl-β-methylcholine injected subcutaneously in patients with hypertension often caused inversion of the T waves of the electrocardiogram in all three leads. Atropine quickly restored the T waves to the upright position. One gram oral doses in the same patients caused no such electrocardiographic change.

Gastro-Intestinal Actions. Acetyl-β-methylcholine in moderate doses causes an increase in tone, amplitude of contraction and peristalsis of all parts of the gastro-intestinal tract (Comroe and Starr, 1933; Molitor, 1936; and others). Vomiting and defecation may occur after larger doses. The drug is a powerful gastric secretogogue and causes an outpouring of acid and pepsin (Gray and Ivy, 1937; Goodman, 1938; Necheles and coworkers, 1938; and others). The gastric secretory response obtained from small doses in dogs with isolated stomach pouches is exactly the same as that charted for carbaminoylcholine in Figure 36. Pancreatic secretory flow apparently is not increased. Atropine counteracts all the motor and secretory gastro-intestinal effects of acetyl-β-methylcholine.

In man, Starr and associates (1933) observed that the subcutaneous injection of 2.5 to 20 mgm of the drug occasionally caused enhanced peristalsis, increased bowel movements and slight nausea. After oral administration, more marked effects were noted and doses of one gram regularly caused increased peristalsis and more frequent defecation. Abbott (1933), in a further study of the actions of acetyl-β-methylcholine on the gastro-intestinal tracts of normal persons by means of balloon and roentgenographic methods, found that the effects on gastric motility varied with the physiological condition of the stomach, contractions being diminished when the stomach was empty and tonus and peristalsis being enhanced when food was present. Both the small and large intestines were stimulated by average subcutaneous doses of the drug. An increase in gastric secretion tended to occur, especially in patients with hypochlorhydria. Oral administration of suitably large doses elicited the same gastro-intestinal responses as did subcutaneous injections of the drug.

Respiratory Effects. Acetyl-β-methylcholine causes bronchoconstriction and increased secretion of the glands of the respiratory mucosa. Both atropine and epinephrine overcome the bronchospasm. In man, Starr and associates (1933) observed that subcutaneous injection of the drug caused no significant effect on respiration except a transitory increase in the depth of breathing. No râles were noted, although in some patients coughing occurred. Occasionally, a sensation of "pressure" or "constriction" under the sternum was complained of, perhaps attributable to bronchospasm, or to spasm of the cardia or esophagus. In one of their subjects, an attack of typical bronchial asthma immediately followed the injection of the drug. Inquiry revealed that this subject had a history of asthma. Oral administration of acetyl-β-methylcholine produced no changes in respiration in any of the persons studied. Hurtado and Kaltreider (1934) observed that the subcutaneous injection of 15 mgm of the drug in two normal young adults decreased the vital capacity between 15 and 20 per cent, at the height of action, the decrease affecting chiefly the complementary air. A sense of substernal constriction was noted by both patients.

Glandular Effects. All glands innervated by cholinergic nerves are stimulated by acetyl-β-methylcholine, and therefore lacrimation, salivation and sweating are prominent objective manifestations of the action of the drug. The secretory responses noted in man after a subcutaneous injection of 20 mgm are charted in Figure 35. Sweating is often so pronounced that the underclothing becomes drenched and the normal rate of salivary flow may be increased ten-fold or more. Sweating and salivation, but not lacrimation, occur after large oral doses and are much less prominent than after parenteral injection. The general and local sweating responses of human beings to acetyl-β-methylcholine have also been investigated by Myerson and associates (1937). They found that the generalized sweating caused by subcutaneous administration of the drug was inhibited by atropine and enhanced by prostigmine or eserine. The local sweating response induced by intradermal injection of acetyl-β-methylcholine is likewise inhibited by atropine but also by epinephrine, as a result of the vasoconstriction caused by the latter drug. The local sweating response varied considerably in different individuals. The sweat produced was alkaline to litmus and the alkalinity increased as the response proceeded. In hypertensive patients, Page (1935) noted that the sweating and flushing, which always occurred in the same areas and paralleled each other in intensity, did not extend to the hands and feet. The clinical investigations of List and Peet (1938) on the sweating mechanism of patients with various types of sympathectomies and peripheral nerve lesions and their diaphoretic response to pilocarpine and acetyl-β-methylcholine are presented on page 390.

Urinary Tract. The general vasodilatation which follows administration of acetyl-β-methylcholine to animals does not extend to the renal vascular bed (Comroe and Starr, 1933), both kidney and urine volume being diminished. The detrusor muscle of the urinary bladder is caused to contract by acetyl-β-methylcholine. In cats with neurogenic bladders due to experimental lesions of the sacral roots and spinal cord, Levin (1938) demonstrated satisfactory evacuation of the bladder following injection of the drug.

In six patients with normal urinary tracts, the effects of acetyl-β-methylcholine were investigated by Loman and coworkers (1938) by means of urographic studies. Given subcutaneously in doses of 20 mgm, the drug caused the kidney shadow to diminish as much as three to four cm. in size. The pelves and calyces became narrowed, the ureters were constricted and showed marked peristalsis and the bladder was contracted markedly, triangular in shape with flattened top and evidenced increased trabeculation. Prostigmine in doses of 0.5 mgm was ineffective but enhanced the urinary effects of small doses of the choline ester so that five mgm of the latter produced the responses listed above.

Miscellaneous Actions. Acetyl-β-methylcholine has practically no effect upon the size and shape of the human *gall bladder* when administered subcutaneously in adequate doses. Indeed, in the majority of cases, the drug causes an inhibition of normal emptying of the gall bladder following the ingestion of a fat meal (Schube and coworkers, 1938). In anesthetized cats, large doses of the ester cause an increase in intrabiliary pressure (Flexner and associates, 1938), but this may be secondary to contraction of the duodenum at the point of entrance of the common bile duct. The *cerebrospinal fluid pressure* is elevated in man after subcutaneous injection of acetyl-β-methylcholine (Myerson and coworkers, 1937), probably a result of the cerebral vascular dilatation. *Skeletal muscle* power is enhanced by administration of acetyl-β-methylcholine to patients with myasthenia gravis (Fraser and coworkers, 1937).

Chemistry and Preparations. The structural formula of acetyl-β-methylcholine is presented on page 351. Its close chemical relation to the other choline esters is evident as well as its relation to muscarine. The drug is available as the chloride or bromide salt.

Acetyl-β-methylcholine Chloride (*Mecholyl; Mecholin*). This compound is not official and is not described in N.N.R. (*see* Report of the Council, 1935). It consists of a white, odorless, bitter, and very deliquescent crystalline powder which is very soluble in water and alcohol. It is decomposed by alkalis. Aqueous solutions are fairly stable to heat and deteriorate slowly on standing. The drug should be kept in tightly stoppered containers. Market preparations include sterile ampules containing 25 mgm each of the dry powder, and sealed vials containing either one or 10 grams of the drug.

Acetyl-β-methylcholine Bromide (*Mecholyl Bromide*). This compound is not official and is not described in N.N.R. It consists of a white, bitter, deliquescent powder which is very soluble in water and alcohol. It is decomposed by alkalis but is fairly stable in aqueous solution. The drug is marketed for oral use in tablets containing 200 mgm each.

Routes of Administration and Doses. *Oral.* In sharp contrast to acetylcholine which is inactive by mouth, large doses of acetyl-β-methylcholine have mild systemic effects when taken orally. The responses appear in from 15 to 75 minutes and are manifested chiefly on the gastro-intestinal tract and peripheral blood vessels. The effective oral dose varies considerably, and although the initial dose is from 50 to 100 mgm, repeated several times daily, amounts as large as 500 mgm to 1.5 grams may have to be given to obtain demonstrable effects. It is apparent that these doses are enormously higher (50 to 100 times higher) than the effective hypodermic dose, due to the destruction of the drug by the gastro-intestinal enzymes and the alkalinity of the intestinal contents. For this reason, oral administration is often unsatisfactory, and the results obtained may be capricious and undependable. Epigastric distress and nausea due to local gastric irritation are usually avoidable by giving the drug in milk.

Subcutaneous. This is the preferred route of administration of acetyl-β-methylcholine for most purposes. The drug is given in aqueous solution and the dose depends on two factors, the results desired and the patient's age. As a rule, the older the patient the larger must be the dose in order to obtain a given effect. The range of dosage varies from 2.5 to 40 mgm or more. It is highly advisable to test the patient's reaction to the smaller doses before resorting to larger ones. When giving the drug by the subcutaneous route, three methods are available for controlling the results obtained with any given dose. First, massage of the site of injection will greatly facilitate absorption. Secondly, a tourniquet applied to the site of injection will delay absorption and allow rapid recovery from effects of the drug which are untoward or greater than desired. Thirdly, the intravenous injection of from 0.5 to 1.0 mgm of atropine will arrest completely and immediately all the muscarinic responses to acetyl-β-methylcholine, and it is recommended that a sterile solution of atropine be kept at hand ready to inject in an emergency. By the methods suggested above, one can control the intensity of action of acetyl-β-methylcholine with a nicety rarely possible with other drugs.

Iontophoresis. In the therapy of peripheral vascular disease, chronic ulcers, arthritis, etc., acetyl-β-methylcholine may be administered by iontophoresis. The drug, like alkaloids, takes a positive electric charge and can thus be carried into the tissues if it is applied to the positive electrode of a galvanic current. For this purpose, an aqueous solution of 0.25 to 1.0 per cent is used to wet an asbestos or cotton pad placed under the positive electrode (malleable metal plate) of a galvanic machine (not diathermy). The dispersive electrode may be applied to the back, a large moist pad being suitable. A current of from 20 to 50 milliamperes is employed for from 20 to 30 minutes, both starting and stopping of the current being performed gradually. The drug should not be applied directly over an ulcerated area of the skin until a firm scab has formed over it. Treatments are usually given two or three times weekly. General reactions are similar to those observed after subcutaneous administration of the drug and can be controlled by reduction of the intensity of the current. Local effects at the site of application of the solution of acetyl-β-methylcholine include warmth, flush, sweating, elevation of skin temperature, and punctate rash, occasionally resembling rose spots. The special technic and apparatus necessary for iontophoresis usually place the procedure beyond the scope of the general practitioner.

Nasal. Systemic effects have been observed in man from the application of strong solutions (25 per cent) of acetyl-β-methylcholine to the nasal mucosa (Van Dellen, Bruger and Wright, 1937), but this route of administration is reserved for the treatment of local affections of the nasal mucous membranes (*e.g.*, ozena).

Clinical Toxicity. A number of the untoward reactions seen clinically after the administration of acetyl-β-methylcholine have been mentioned, but they may profitably be summarized here. Death has not been reported from use of the drug. In one case, a dose ten times the therapeutic gave an alarming but transient syncopal reaction with cardiac arrest and loss of consciousness. In another instance, a full therapeutic dose by error was given intravenously and cardiac asystole occurred for 70 seconds. Complete recovery ensued although the electrocardiogram remained very different from that present before the accident. Nausea and vomiting are usually the first signs of overdosage. Asthmatic attacks may be precipitated, especially in those individuals susceptible to asthma. For example, in 15 asthmatic patients injected subcutaneously with from 20 to 40 mgm of acetyl-β-methylcholine, Villaret and coworkers (1934) noted the occurrence of typical asthmatic attacks in all instances. Substernal pressure or pain has been reported, but whether it is due to bronchoconstriction or spasm of the esophagus or cardia is not known. It seems unlikely that the pain is due to coronary vasoconstriction. Dyspnea may also develop, but it is transient and of no consequence. Fainting may occur if the patient assumes a vertical position during the height of action of the drug. Involuntary defecation may be noted after large doses. Transient complete heart block has been recorded and in individuals with hyperthyroidism the compound has been known to produce a short period of auricular fibrillation. Patients with hypertension may react to the drug with a precipitous fall in blood pressure. Chronic toxicity does not ensue from repeated use of the drug.

Treatment consists of the injection of atropine (0.5 to 1.0 mgm) intramuscularly or intravenously, dependent on the urgency of the case. The patient should be kept recumbent. If an asthmatic attack persists, epinephrine may be needed. Avoidance of most toxic side-actions can be achieved by observing the contraindications and precautions listed.

Contraindications and Precautions. Acetyl-β-methylcholine should never be given by the intravenous route. The dose varies with age, and young adults are quite susceptible to the effects of the drug. Large doses should not be employed until smaller amounts have proved ineffective. Acetyl-β-methylcholine should not be combined with eserine or prostigmine unless there is some impelling reason for doing so and unless the dose of each has been reduced. For example, the prior administration of 0.5 mgm of prostigmine allows five mgm of the choline ester to elicit an intensity of response usually observed only after doses of 20 to 25 mgm. The ester should be given with considerable caution, if at all, to patients with a history of asthma. A sterile solution of atropine should be kept at hand ready for immediate injection if untoward reactions occur which necessitate antidotal therapy. The administration of the drug by iontophoresis should be undertaken only by those thoroughly acquainted with the technical aspects of the procedure. Patients receiving injections of acetyl-β-methylcholine should be in bed and lying down. A bed pan should be provided in the event that the drug makes it necessary to defecate, because assumption of the erect posture during the height of drug action is likely to result in fainting. Hyperthyroid patients should not receive acetyl-β-methylcholine because of the possibility that auricular fibrillation may occur.

Therapeutic Uses

Therapeutic applications of acetyl-β-methylcholine have made use chiefly of the cardiovascular and gastro-intestinal actions of the compound. Thus the drug has been employed successfully in paroxysmal auricular tachycardia, in certain peripheral vascular diseases and in patients with intestinal distention. However, a variety of other uses has received clinical trial.

Disorders of Cardiac Rhythm. *Paroxysmal Tachycardia.* In some patients, reflex vagal stimulation, as, for example, through the carotid sinus mechanism, ocular pressure or the induction of emesis, has long been known to be capable of arresting attacks of paroxysmal tachycardia of auricular or supraventricular origin. Similarly, a large number of such attacks may be relieved quickly by the use of acetyl-β-methylcholine. The most extensive clinical investigations of the efficacy of the drug in this type of arrhythmia have been conducted by Starr (1933, 1936). He was able to bring the attack to an abrupt end in 66 (88 per cent) of 75 attacks in 37 patients. Alternate pressure over the carotid sinus is first performed, a procedure effective in about one-third of the patients. If this is unsuccessful, acetyl-β-methylcholine is administered subcutaneously. The patient should be in bed and forewarned that he may experience deep breathing, warmth, sweating, salivation, intestinal hyperactivity, etc. A bed pan and atropine should be at hand. The dose is adjusted according to both age and weight. Whereas a young adult may respond successfully to 15 to 30 mgm of the drug, an individual over 50 years of age may require from 40 to 50 mgm or more in order to establish normal rhythm. This is evidently related to the ability of the heart to respond to cholinergic stimulation, a phenomenon also noted with regard to atropine. Obese patients require larger doses than do slender ones. If quinidine is being prescribed for the disorder, the choline ester will not revert the rhythm to normal unless the dose of the former drug is small and the dose of the latter large.

If the arrhythmia does not cease promptly at the height of the flush after the administration of the drug, the injection site should be massaged vigorously and the carotid sinuses alternately compressed. Failure to employ these auxiliary measures decreases markedly the percentage of successes. If the disorder persists, a second injection may be given as soon as the effects of the first have subsided, that is, in about twenty to thirty minutes. The second dose is increased and pressure on the carotid sinus is exerted at the height of action of the drug, as denoted by the facial flush. The attack is usually terminated within a minute or two after the drug is injected. The transition period between the paroxysmal tachycardia and the establishment of normal sinus rhythm is characterized by a brief cardiac pause, followed by a momentary irregularity of the rhythm and intensity of heart sounds and of the pulse. Side-effects from acetyl-β-methylcholine are usually slower in appearing and milder in character in patients with paroxysmal tachycardia than in normal persons receiving the same dose (Starr, 1933).

Acetyl-β-methylcholine is useful only to terminate and not to prevent the occurrence of attacks of paroxysmal tachycardia. For the latter purpose, quinidine is the agent of choice. Although acetyl-β-methylcholine produces side-effects disagreeable to the patient, the temporary discomfort is a small price to pay for the relief the drug brings from the distress of the attack. Repeated use of acetyl-β-methylcholine does not impair its efficacy. For example, Wright (1938) reported that the drug (in doses of five to 40 mgm) was immediately successful in stopping 15 of 16 attacks of paroxysmal tachycardia of auriculoventricular nodal origin recurring in a child over a two year period.

Other Arrhythmias. In *auricular flutter,* the ester is rarely successful in restoring the rhythm to normal. The flutter may be converted to auricular fibrillation (Nahum and Hoff, 1935; Starr, 1936) either before or without a return to a normal sinus mechanism. Although the grade of block is often increased and the ventricular rate thereby slowed, the improvement usually is transitory and passes with the subsidence of the action of the drug. However, the differential diagnosis between paroxysmal tachycardia and certain cases of auricular flutter can occasionally be made by taking an electrocardiogram at the height of action of acetyl-β-methylcholine and observing the arrhythmia when the auriculoventricular block is obvious. In patients with *auricular fibrillation,* acetyl-β-methylcholine does not restore a normal sinus mechanism. The ventricular rate may be slowed temporarily but this is of no therapeutic significance. The drug is contraindicated in *tachycardia secondary to hyperthyroidism,* does not slow the rate, may even increase it, and occasionally produces transient fibrillation of the auricles.

Peripheral Vascular Diseases. The effects of acetyl-β-methylcholine on the peripheral vessels and skin temperature have already been described. Attempts have been made to utilize these actions in the therapy of a variety of peripheral vascular diseases. For this purpose, it is necessary to administer the compound in such a manner as to obtain maximal effects on the peripheral vessels for long periods of time and unassociated, if possible, with untoward actions on other functions of the body. Thus, the drug is administered either orally or by iontophoresis.

In *Raynaud's disease,* Starr (1933) studied the response to acetyl-β-methylcholine in four patients. He found that the drug did not prevent the development of vascular spasm when the hands were exposed to severe cold, and did not cause prompt relaxation of the spasm so produced. However, it was capable of overcoming or preventing spasm induced by moderate exposure. In three patients to whom the drug was given orally in doses of from 20 to 100 mgm or more three times daily, a definite measure of relief was experienced from spasm encountered by exposure to cold or during their usual occupations. Striking benefit in 12 patients with Raynaud's disease was obtained by Kovacs and associates (1936) as a result of local iontophoresis. Increased warmth, improved color of the hands and feet, a decrease in the number and severity of attacks during the winter months, and complete healing of painful ulcerations were observed. The syndrome definitely improved despite the complicating factor of scleroderma in six patients.

In patients with *thromboangiitis obliterans* or *arteriosclerosis obliterans,* the organic occlusion of the peripheral vessels precludes great beneficial effect of acetyl-β-methylcholine unless there is an associated factor of vascular spasm. Kovacs and coworkers (1936) thus noted that only those individuals with an appreciable factor of vasospasm responded satisfactorily to therapy with the choline ester, and in these patients there was observed healing of ulcerations and increased exercise tolerance before the appearance of claudication. Starr (1933) found that oral administration of the drug in doses of from 200 to 500 mgm relieved pain and promoted healing in areas of threatened gangrene in at least two of four patients with occlusive peripheral vascular disease. The subcutaneous route is contraindicated, and large oral doses may be needed before relief is obtained. In all cases of thromboangiitis obliterans, Kramer (1937) observed that iontophoresis with acetyl-β-methylcholine resulted in definite improvement in three, some benefit in three, temporary relief in two and failure in three. In eight patients with diabetes mellitus and peripheral arteritis, five showed improvement.

Other disorders related to the integrity of the peripheral circulation have been reported to show improvement after therapy with acetyl-β-methylcholine. These include *phlebitis, varicose* and other *ulcers,* etc. (Starr, 1933; Kovacs and associates, 1936; Kramer, 1937; and others). Saylor and associates (1936) have had particularly successful results in patients with chronic varicose ulcers, healing occurring in 23 of 26 consecutive unselected patients, and they recommend iontophoresis therapy for those ulcers occurring in patients in whom sclerosing injections are contraindicated or have failed, as, for example, in persons with phlebitis or diabetes.

Gastro-Intestinal Disorders. Acetyl-β-methylcholine has been successfully employed in patients with *abdominal distention* due to postoperative intestinal ileus, anesthesia, acute infectious diseases, etc., although the advent of prostigmine has decreased the frequency of its employment. It is administered by the subcutaneous route in doses of 10 to 20 mgm (Abbott, 1933). Pain may be exaggerated temporarily due to resumption of intestinal activity, and insertion of a rectal tube may be necessary to permit expulsion of the gas. Occasionally, the drug acts when other measures such as an inlying rectal tube, medicated enemas, hot fomentation, turpentine stupes, prostigmine, posterior pituitary, etc., have failed; but it is probably best to reserve its use for patients in whom the more usual and milder procedures have been tried.

In patients with *atonic constipation,* the oral use of large doses of acetyl-β-methylcholine may allow comfortable laxation and a satisfactory increase in the frequency of stools. The drug has also been administered orally with promising results to children with *megacolon* (Law, 1940). Similarly, the drug may be employed to test the functional ability of the musculature of the colon prior to surgical intervention in cases of congenital megacolon.

Urinary Tract Disturbances. Acetyl-β-methylcholine has been employed to aid evacuation of urine and thus avoid catheterization and the attendant risk of uriniary tract infection in patients suffering from postoperative urinary retention or various neurogenic disturbances of the urinary bladder; but the advent of prostigmine and carbaminoylcholine has decreased the use of the compound for this purpose. Langworthy (1936) has reported favorable effects from administration of acetyl-β-methylcholine in tabes dorsalis, and has been able to reduce residual urines of large volume to practically zero. He also found it to be of value in treating acute urinary retention which may occur in tabetics, especially during malarial therapy. Use of the drug has not yielded striking results in bladder dysfunction due to other forms of nervous system injury.

Miscellaneous Uses. In the therapy of arthritis, a number of investigators have apparently obtained favorable results from iontophoresis with acetyl-β-methylcholine. Treatment is not curative but symptomatic improvement may be obtained in a substantial number of cases. Pain, swelling, stiffness and muscular fatigue are reduced and joint function increased. Kovacs and coworkers (1936) reported a series of 117 arthritics observed for from two weeks to two years, treatment being administered twice weekly on the average. Of 44 patients with osteoarthritis, definite improvement occurred in 31; of 73 with rheumatoid arthritis, 50 patients claimed that they were improved. These workers caution that the results are difficult to evaluate, that spontaneous remissions are frequent, that psychological factors are prominent, and that relapses may occur during the course of treatment. Other investigators reporting favorable results in arthritis include Abel (1935), Mathae (1936) and Boyd and associates (1936). The workers last named observed that failures were more prominent in elderly patients suffering from advanced rheumatic arthritis with bone changes and fibrosis, and that those who gained most from the treatment were patients with accompanying circulatory disturbances of the extremities with cool, pale, moist and often cyanotic hands and feet.

Acetyl-β-methylcholine has been employed for a variety of other diseases and symptoms. Patients with *essential hypertension* do not respond favorably to the drug, and acetyl-β-methylcholine does not fulfill the requirements outlined on page 563. Indeed, the drug may cause untoward reactions in hypertensive individuals. It was mentioned previously that favorable results have been reported in *scleroderma* (Kovacs and collaborators, 1936). Duryee and Wright (1937) have also obtained improvement in their patients and record softening and loosening of the skin, healing of ulcerations, return of sweating and hair to the affected parts and occasionally increased visibility of capillaries. In *myasthenia gravis,* muscle power improves (Fraser and coworkers, 1937), but prostigmine and other measures are to be preferred. In *ozena,* local application of a solution of the drug to the nasal mucosa has apparently afforded relief. Prostigmine has also been employed for a similar purpose. Acetyl-β-methylcholine has also been employed in patients with *Ménière's disease, tobacco amblyopia, glaucoma, migraine, cerebrovascular spasm, post-lumbar puncture headache, acrodynia, hypochlorhydria,* etc., but the rationale is not always evident nor is the alleged improvement always due to the drug.

An interesting diagnostic application of the parasympathomimetic actions of acetyl-β-methylcholine is in the detection of *atropine poisoning* (Dameshek and Feinsilver, 1937). If a patient is suspected of having poisoning due to the belladonna alkaloids, 10 to 30 mgm of the choline ester may be injected subcutaneously. The failure of appearance of the characteristic flush, sweating, lacrimation, rhinorrhea, salivation, enhanced peristalsis, etc., is pathognomonic of belladonna intoxication and the diagnosis can thus be made with certainty in otherwise doubtful cases.

CARBAMINOYLCHOLINE

Carbaminoylcholine is another synthetic derivative of choline. It was first prepared by Kreitmar in 1932 and its pharmacological properties have been investigated particularly by Noll (1932), Dautebrande (1933), Simonart and Simonart (1935), Molitor (1936) and Starr (1937). The drug was introduced into therapeutics as a substitute for acetylcholine and under certain circumstances is to be preferred to acetyl-β-methylcholine.

Chemistry and Preparations. The chemical structure of carbaminoylcholine is shown on page 351, and the relationship between its structure and pharmacological action has already been discussed. The drug is available for clinical use in the form of its chloride salt.

Carbaminoylcholine Chloride (Carbamylcholine Chloride; Doryl; Lentin) is not an official preparation and is not described in the N.N.R. It consists of a white, odorless crystalline powder, stable in air and in aqueous solution even when heated. The drug is soluble in water 1:1 to give a solution neutral to litmus. Carbaminoylcholine chloride is available in tablet triturates for oral use (0.2 and 0.4 mgm) and in hypodermic tablets (0.2 and 0.4 mgm). It is also supplied as a powder for preparation of solutions for application to the conjunctiva or nasal mucosa.

Pharmacological Properties. Carbaminoylcholine is a powerful parasympathomimetic agent and differs from acetyl-β-methylcholine especially in being much more stable in body fluids and possessing nicotinic actions on autonomic ganglia. The drug is not susceptible to destruction by cholinesterase and therefore its activity is neither enhanced nor prolonged by eserine or prostigmine (Figure 33). Although selective affinities of the drug for particular organs are not readily demonstrable in animals (Molitor, 1936), the results obtained from its administration to human beings suggest that the drug has a greater action on the gastro-intestinal tract and urinary bladder and less action on the heart than is the case with acetyl-β-methylcholine. Some of the major characteristics of the drug in comparison with allied choline derivatives are shown in Table 19.

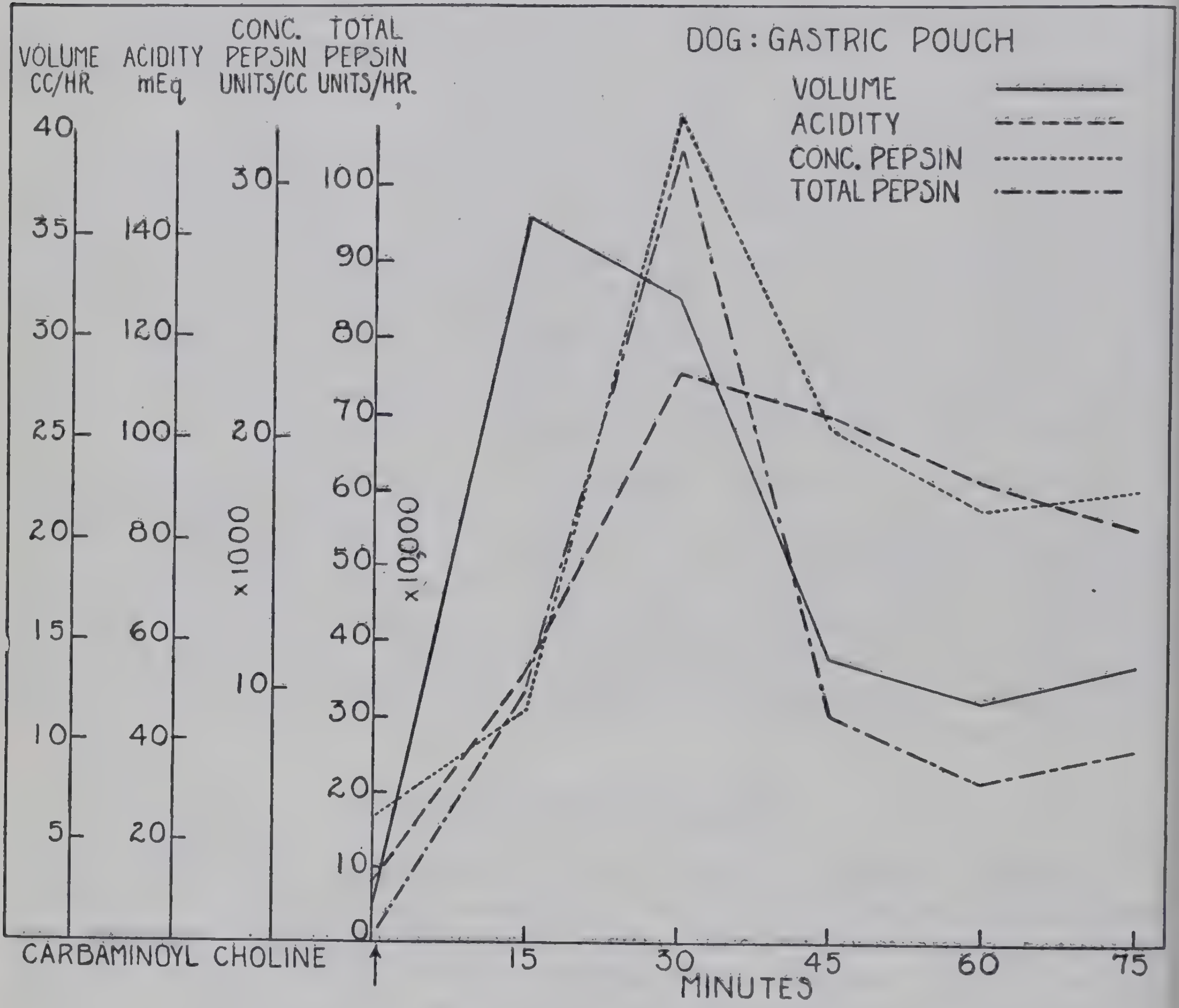


FIGURE 36. *The effect of carbaminoylcholine (doryl) on the gastric secretion of an isolated stomach pouch in a dog.*

Pepsin unitage: one cc of a one per cent solution of 1:10,000 pepsin equals 1000 units. Note factors for multiplication in pepsin scales. A fasting sample was taken at zero time, after which 0.008 mgm of doryl per kilo was injected subcutaneously and samples collected at 15 minute intervals. Note that the secretion of all components of the gastric juice is markedly stimulated, especially pepsin. This response to doryl can be antagonized by atropine.

In *animals,* marked stimulation of all structures innervated by cholinergic nerves occurs as a result of the administration of adequate amounts of carbaminoylcholine. Thus there is seen a fall in blood pressure, bradycardia, peripheral vasodilatation, sweating, lacrimation, salivation, miosis, increased peristalsis, contraction of the uterus and urinary bladder, skeletal muscular stimulation and a rise in blood pressure after atropine (nicotinic action). All the muscarinic effects listed are antagonized by atropine. Carbaminoylcholine is the most potent and also the most toxic of the known derivatives of choline, but its margin of safety in clinical use is practically identical with that of acetyl-β-methylcholine. Inasmuch as carbaminoylcholine is not destroyed by the cholinesterase of tissue and blood, its therapeutic potency and toxicity are not affected by the combined administration of anti-esterase drugs such as eserine and prostigmine. This is in

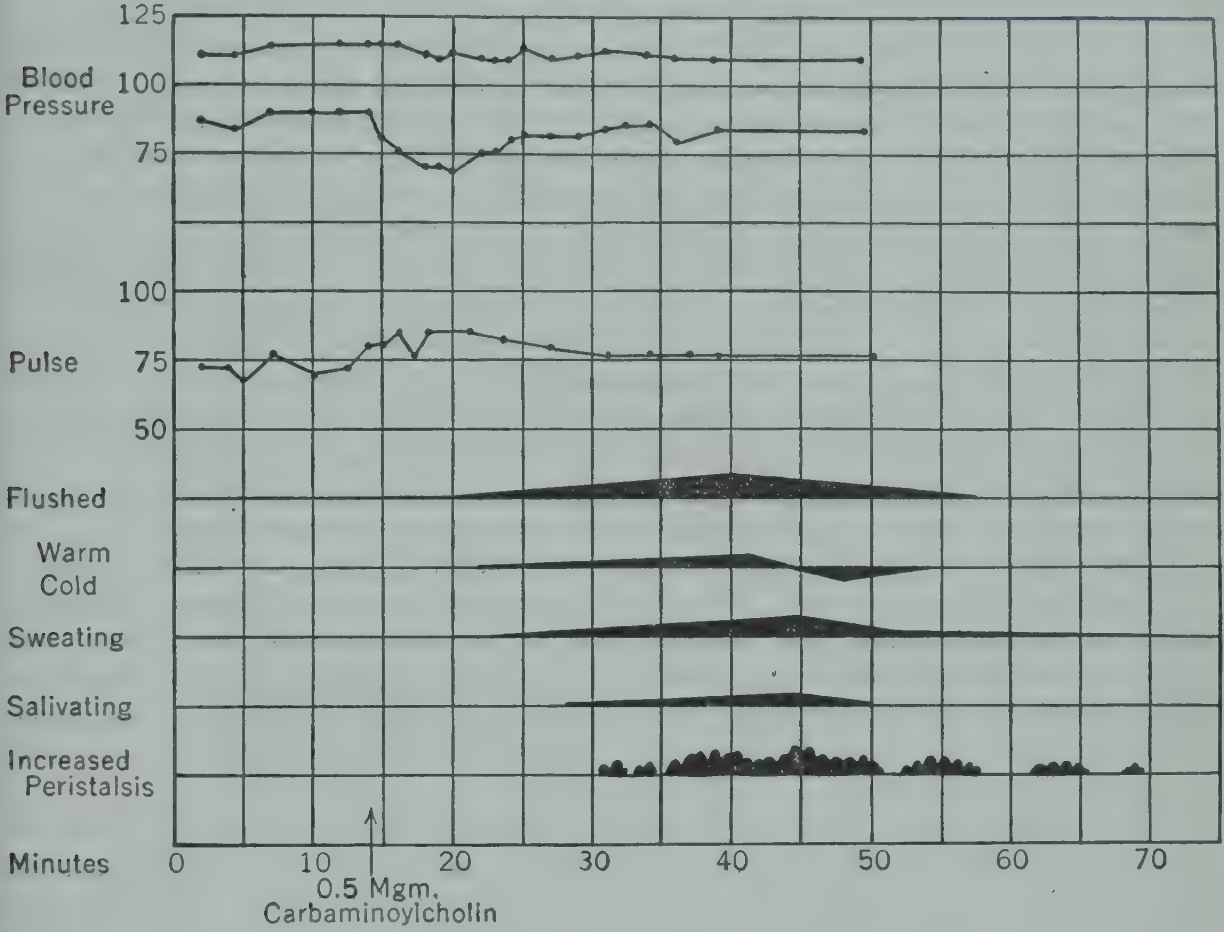


Figure 37. *The effects of carbaminoylcholine in man.*

Normal young adult, recumbent posture, 0.5 mgm carbaminoylcholine chloride injected subcutaneously at zero time after a preliminary rest period. The diastolic blood pressure begins to fall within a minute or two and reaches its lowest level within six minutes, at which time the pulse rate shows its maximal acceleration. These two effects are never marked and recede within the following ten minutes. Flushing, a sensation of warmth, and sweating appear only after six minutes or more from the time of injection, develop gradually and are never as prominent as after acetyl-β-methylcholine. Salivation is even less noticeable. About 15 minutes after the administration of carbaminoylcholine, borborygmus is usually noted, increases in intensity and is sometimes accompanied by cramps. The height of action of the drug is reached in from 20 to 30 minutes, at a time when the effects of acetyl-β-methylcholine would have already disappeared (see Figure 35). The actions wear off gradually and disappear after approximately one hour. See text for the signs and symptoms produced by the drug. (After Starr, 1937. Courtesy of the *American Journal of the Medical Sciences.*)

sharp contrast to acetylcholine and acetyl-β-methylcholine. If the dose is properly selected, certain pharmacological actions can be elicited with doses which do not evoke others. For example, the drug produces marked stimulation of all constituents of the gastric juice in doses which cause few other discernible effects. In dogs with isolated gastric pouches, carbaminoylcholine can readily be shown to be the most potent secretogogue of the choline group of drugs, and in particular it is the most potent peptogogue known (Goodman, 1938). A typical gastric secretory response to the drug is shown in Figure 36.

The effects of carbaminoylcholine in *man* have been studied especially by Starr (1937) who tested the actions of oral (0.4 to 1.0 mgm) or subcutaneous (0.1 to 1.0 mgm) doses in a group of 26 normal young adults. The typical responses elicited by a subcutaneous injection of 0.5 mgm of carbaminoylcholine are depicted in Figure 37, which may profitably be compared with Figure 35. It will be noted that the actions appear more slowly and gradually than after the injection of acetyl-β-methylcholine and last much longer. Warmth and flushing of the face are the first evidence of action of the drug. Sweating, lacrimation and salivation occur later and are not nearly as prominent as after acetyl-β-methylcholine. Audible peristalsis and occasionally intestinal cramps appear after 15 to 20 minutes, and a desire to urinate may be experienced by some subjects. The diastolic pressure often but not always falls slightly and the pulse rate rises somewhat, these effects occurring early. Palpitation and respiratory effects do not ensue. After injection of larger doses (1.0 mgm), the actions still come on slowly and are similar to those outlined above. The blood pressure and pulse changes are not more marked but the remaining actions are prominent, abdominal cramps being so uncomfortable that atropine has to be administered. As a rule, the largest doses which can be tolerated cause severe intestinal effects before the blood pressure is greatly affected. This is in sharp contrast to the actions of acetyl-β-methylcholine which are prominent on the cardiovascular system at a time when the gastro-intestinal effects are still minimal.

Starr also studied the response to *oral* administration of carbaminoylcholine. A dose of 0.6 mgm causes slight effects, manifest after one hour by the appearance of flushing, sweating, epigastric distress, and belching; after two hours by a sensation of tightness in the urinary bladder and still later by some difficulty in visual accommodation. Changes in the pulse rate and blood pressure are slight. Headache, salivation, and abdominal cramps may appear after large doses. Cumulative effects evidently occur from repeated oral administration, probably indicating the resistance of the drug to destruction in the body, and some patients given 0.4 mgm orally three times daily soon complained that the dose was being increased. The majority of persons, however, are able to tolerate from 0.2 to 0.4 mgm orally once or twice daily without difficulty. Still others are able to take much larger doses without untoward effects. It is clear, therefore, that the actions of the drug are variable and uncertain after oral administration, and a dose producing uncomfortable effects in one patient may be well tolerated by another.

In a more detailed study of the cardiovascular and certain other responses to carbaminoylcholine, Starr and associates (1937) gave 0.5 mgm subcutaneously to six patients, four of whom had peripheral vascular disease and previously had experienced relief from pain after the drug. The average results obtained were as follows (+ = increase; — = decrease): pulse rate, +7.6 per cent; systolic blood pressure, —6.5 per cent; diastolic pressure, —7.2 per cent; cardiac output, +12.3 per cent; stroke volume, +3.7 per cent; left ventricular work per minute, +4.9 per cent; left ventricular work per beat, —2.6 per cent; heart volume, —2.0 per cent; metabolic rate, +3.5 per cent; arteriovenous oxygen difference, —5.5 per cent; respiratory volume, +5.6 per cent; peripheral vascular resistance, —16.6. Only the effects on blood pressure, pulse rate and respiratory volume appear statistically significant. The above data do not indicate that carbaminoylcholine has a stimulant or depressant effect on the human heart in the doses employed. Electrocardiographic studies revealed no changes attributable to the drug.

Whereas atropine prevents or rapidly abolishes all the muscarinic responses to acetylcholine and acetyl-β-methylcholine, it acts more slowly and less effectively in antagonizing the actions of carbaminoylcholine. Thus Starr (1937) found that atropine, given subcutaneously to 12 normal subjects in a dose of 0.6 mgm 20 minutes before an injection of 0.3 mgm of carbaminoylcholine, completely blocked the usual effects of the latter drug. The same dose of atropine greatly diminished the response to 0.4 mgm of carbaminoylcholine, had a slight antagonistic effect on the action of 0.8 mgm, but did not significantly alter the response to 1.0 mgm. Likewise, when the full effects of a large subcutaneous dose of carbaminoylcholine were manifest, the injection of 0.3 mgm of atropine did not significantly diminish their intensity. A dose of atropine of 0.6 mgm under these circumstances caused a slow but definite disappearance of the uncomfortable actions within 30 minutes.

Doses and Routes of Administration. Carbaminoylcholine may be administered orally or subcutaneously. The *oral* dose varies from 0.2 to 0.8 mgm two or three times daily, dependent on the patient's tolerance and the results desired. The single *subcutaneous* dose ranges from 0.2 to 0.4 mgm. It will be noted that the oral dose is not much larger than the subcutaneous, in sharp contrast to the ratio of oral and subcutaneous doses of acetyl-β-methylcholine. This is due to the greater stability of carbaminoylcholine in the intestinal fluids. The drug should not be injected intravenously. In weak solution (0.1 per cent), carbaminoylcholine may be applied locally to the nasal mucosa or conjuctiva. A solution of atropine ready for immediate injection should be at hand to counteract untoward responses to the drug.

Clinical Toxicity. Carbaminoylcholine produces the same toxic effects described for acetyl-β-methylcholine but the relative intensity of these varies somewhat. Patients differ considerably in their response to the drug, especially when it is orally administered. Malaise, headache, abdominal discomfort, nausea, belching, peristaltic waves, colicky pain, diarrhea, flushing, a sensation of heat about the face, asthmatic attacks, and fall in blood pressure are among the prominent reactions which are noted. As stated, the gastro-intestinal actions are more prominent than are the cardiovascular actions. The ordinary therapeutic dose of atropine (0.6 mgm) antagonizes the untoward effects of large doses of carbaminoylcholine much more slowly than those of acetyl-β-methylcholine, and increased amounts of atropine may have to be given to obtain relief.

Therapeutic Uses. Carbaminoylcholine has been employed in several of the syndromes for which acetyl-β-methylcholine has been used, but the drug is relatively new and sufficient clinical data are not yet available properly to appraise its clinical status. Particularly promising reports have appeared concerning its use in patients with peripheral vascular disease and urinary retention.

In patients with *peripheral vascular disease,* the administration of carbaminoylcholine often results in increased peripheral circulation, especially when vasospasm rather than organic occlusion predominates. Rest pain may be strikingly relieved and the healing of areas of threatened gangrene promoted. Inasmuch as oral medication is often unsatisfactory, small doses may be given at intervals by injection. Patients who cannot be kept under medical supervision should receive oral therapy with acetyl-β-methylcholine rather than with carbaminoylcholine.

In a number of clinical reports, favorable results have apparently been obtained from the use of carbaminoylcholine in patients with *urinary retention* occurring after surgical operation, childbirth or anesthesia, or that due to lesions of the spinal cord. Thus the necessity for catheterization with the attendant danger of infection may be circumvented. Great care should be exercised in using the drug in patients who are very ill or in shock. The effective subcutaneous dose is usually 0.25 mgm and it may be necessary to repeat this once or twice at half-hour intervals. Evacuation of the bladder usually occurs in from five to 30 minutes (Moir, 1937; Maxwell, 1937; Officer and Stewart, 1937; Schwartz, 1938; and others).

Miscellaneous Uses. Carbaminoylcholine has not been found effective in the treatment of cardiac arrhythmias, and acetyl-β-methylcholine remains the preferred agent for use in paroxysmal tachycardia. Although the drug causes an acute fall in blood pressure in hypertensive individuals, attempts to lower the elevated blood pressure over a prolonged period have been unsuccessful (Starr, 1937). Carbaminoylcholine increases muscular power in patients with *myasthenia gravis* (Fraser and coworkers, 1937), but prostigmine remains the parasympathomimetic agent of choice in this disease. The choline compound has also been employed locally with varying degrees of success in *ozena* and *increased intraocular tension.*

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CHAPTER 21

DRUGS STIMULATING STRUCTURES INNERVATED BY CHOLINERGIC NERVES (PARASYMPATHOMIMETIC DRUGS)

II. INHIBITORS OF CHOLINESTERASE: PHYSOSTIGMINE (ESERINE) AND PROSTIGMINE

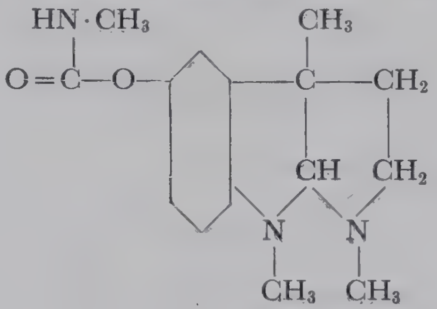
PHYSOSTIGMINE (ESERINE)

History and Source. Physostigmine, also called eserine, is an alkaloid obtained from the Calabar or ordeal bean, the dried ripe seed of *Physostigma venenosum,* a perennial woody climber growing on the banks of streams in tropical West Africa.

These beans were once used by the native tribes as an "ordeal poison" in trials for witchcraft. If the usual symptoms of poisoning developed, the victim was pronounced guilty. It is said that the innocent person, unafraid of the ordeal, would eat the poison rapidly. Vomiting from gastric irritation would ensue and automatic protection was thus afforded. The guilty person, afraid of the trial, would partake slowly of the bean and poisoning rather than emesis would result.

Although the calabar beans were known in England in 1840, their properties were not investigated until a number of years later. In 1863, Fraser noted that extracts of the bean caused pupillary constriction. In the following year, the pure alkaloid, physostigmine, was isolated by Jobst and Hesse. The first extensive studies on the pharmacology of the pure alkaloid were those of Harnack and Witkowski in 1876.

Chemistry, Preparations and Doses. Although several alkaloids have been isolated from the Calabar bean, the most important one is physostigmine. The chemical structure of this substance is as follows:



Physostigmine

The official preparation is *Physostigmine Salicylate (Eserine Salicylate),* U.S.P., B.P., consisting of colorless bitter crystals which are soluble in water (1:75). The salt and its aqueous solutions in glass containers oxidize upon exposure to air and light and turn first a pink and then a reddish-brown color due to the formation of rubreserine. These colored solutions are decomposed and should not be employed. Addition of boric acid will prevent the decomposition. The average adult oral dose of physostigmine salicylate is 2.0 mgm; the hypodermic dose, 0.5 to 1.0 mgm. *Lamella of Physostigmine* is official in the B.P., each disc containing 0.065 mgm of the alkaloid.

The relationship between the chemical structure of physostigmine and its pharmacological properties is discussed under prostigmine.

Mechanism of Action. Physostigmine exerts its pharmacological activity in the body by inhibiting cholinesterase in body fluids and tissues (page 339). This esterase is responsible for the rapid and continuous destruction of acetylcholine, whether the latter is produced physiologically as the result of cholinergic nerve impulses or injected into the body by the physician. Physostigmine preserves acetylcholine from enzymatic hydrolysis and its pharmacological effects may be accounted for on this basis. One may expect, therefore, that the responses to physostigmine would be detectable only in those structures innervated by cholinergic nerves, and that the drug would be inactive in the absence of acetylcholine. Both of these propositions are true.

By preventing the rapid hydrolysis and inactivation of acetylcholine, physostigmine allows the latter to exert, in an intensified manner, all of its characteristic actions. These include not only the muscarinic effects of acetylcholine on smooth muscles, glands and the heart, but also the nicotinic actions of acetylcholine on skeletal muscles and autonomic ganglia. This accounts for the fact that the actions of physostigmine are not always entirely predictable, as are those of muscarine and pilocarpine which possess only muscarinic properties. The effects of physostigmine on ganglia, for example, may antagonize or occasionally supersede those on the more peripheral effector organs. This is particularly evident in the cardiovascular responses to physostigmine. The preservation of acetylcholine by physostigmine peripherally at cholinergic nerve endings in the heart and in smooth muscles of blood vessels will tend to cause bradycardia, vasodilatation and lowering of blood pressure, whereas the same property of the drug exerted in sympathetic ganglia will cause tachycardia, vasoconstriction and an increase in blood pressure. In addition, physostigmine preserves acetylcholine liberated by splanchnic nerve impulses to the adrenal medulla (page 332), and thus increases the discharge of epinephrine. The epinephrine, in turn, antagonizes the muscarinic effects of physostigmine.

When the cholinergic nerves to an organ are resected and degenerate, acetylcholine can no longer be locally liberated as the chemical mediator (page 341). Under these circumstances, physostigmine fails to manifest its characteristic effects. This is clearly seen, for example, in the denervated iris where physostigmine normally causes miosis. Likewise, when skeletal muscle is deprived of its spinal motor innervation, physostigmine loses its ability to cause typical fibrillary twitching. Although cholinesterase is inhibited, there is no substrate (*i.e.*, acetylcholine) to be protected. Under certain circumstances, the administration of physostigmine will produce contraction in denervated skeletal muscle, but in such an instance it is possible to demonstrate that acetylcholine is being produced locally by other cholinergic nerves, namely, the cholinergic vasodilator fibers to blood vessels in the muscle.

It is claimed by some workers that physostigmine, in addition to acting through its anticholinesterase property, also exerts a direct effect on muscle and gland cells. The strongest evidence for this view comes from the studies on the relationship between cholinsterase inhibition and physostigmine action. It has been shown, for example, that after the alkaloid has depressed serum cholinesterase activity to a given low level, additional amounts of drug will continue to cause responses of effector organs proportionate to the dose without further depression of esterase activity. The obvious objection to these experiments, however, is that serum cholinesterase is being studied rather than tissue cholinesterase, and in the last analysis it is the titer of tissue esterase which determines the rate of acetylcholine hydrolysis and the effectiveness of physostigmine. Unfortunately, little is known of the quantitative aspects of the inactivation of tissue esterases by physostigmine.

Atropine prevents the muscarinic effects of physostigmine; curare and nicotine, the nicotinic effects. Theoretically, at least, an atropinized, curarized and nicotinized animal should be completely protected against the responses to physostigmine. These autonomic blocking drugs prevent the effector cells from responding to the acetylcholine preserved by the anticholinesterase action of physostigmine.

Physostigmine Specificity for Cholinesterase. Although a number of drugs and other chemical agents can be shown to inhibit cholinesterase activity, none of these can compare in potency or specificity with physostigmine and related compounds. A number of enzymes exist in the body which are capable of hydrolyzing various esters, but physostigmine and prostigmine selectively inhibit only that enzyme which is concerned with the destruction of acetylcholine, namely, cholinesterase. For example, the injection of one mgm of physostigmine in man reduces the cholinesterase activity of serum by about 15 per cent (Jones and Tod, 1935). In dogs, intravenous physostigmine (0.1 mgm per kg) reduces the activity of the serum esterase almost instantaneously by 75 to 90 per cent (Hall and Ettinger, 1937). Comparable data are available for prostigmine. Physostigmine does not destroy cholinesterase but merely inactivates it temporarily by loosely combining with it. This union can be broken in various ways with a resulting restoration of full enzymatic activity. *In vitro,* this can be accomplished by dialyzing physostigmine free from its combination with cholinesterase. In the body, physostigmine is released from combination with the enzyme by destruction of the drug and by its excretion in the urine.

Pharmacological Actions

In view of the mechanism of action of physostigmine, it should be possible to predict the pharmacological properties of the alkaloid merely by knowing those loci where acetylcholine is physiologically released by nerve impulses and the responses of the corresponding end-organs to the chemical mediator. In the main this is true, but several factors prevent the rigid application of such an assumption. As was stated previously, the final response of autonomic structures to physostigmine depends on the balance between the ganglionic and peripheral components of its action. Again, some organs which respond phasically rather than continuously to nerve impulses will not have a constant supply of acetylcholine to be protected by physostigmine. Also, little is known concerning the esterases in various tissues of the body in health and disease or the relative ease with which they are inactivated by physostigmine. Thus, when a *therapeutic* dose of the drug is given to man, the actions on the pupil and bowel are more prominent than those on voluntary muscle, which may show no reaction. On the other hand, when this same dose is given to a patient with myasthenia gravis, marked therapeutic benefit may be obtained from the effects on skeletal muscle. Finally, physostigmine may act to block ganglia and motor end-plates by preserving acetylcholine to such an extent that the paralyzing phase of the nicotinic actions of acetylcholine is brought into play (page 339).

The main therapeutic effects of physostigmine are concerned with the *pupil, intestine* and *skeletal muscle.* Most of the other responses are mainly of toxicological interest.

Eye. When applied locally to the conjunctiva, physostigmine causes pupillary constriction and spasm of accommodation. The intraocular pressure falls. Miosis is manifest in a few minutes and becomes maximal in one-half hour. The pupil gradually returns to its normal size within a period varying from one day to several days. Although the pupil is pin-point in size after physostigmine and smaller than that normally obtainable by the strongest light, it contracts ever further when exposed to weak light. The spasm of accommodation, which may cause macropia, is rather transient and usually disappears in three hours. The fall in intraocular tension is particularly marked in cases when this pressure is elevated, and results mainly from the miosis, a factor which facilitates the resorption of the aqueous humour.

Gastro-intestinal Tract. Physostigmine increases the tone and motility of the gastro-intestinal tract. Peristalsis is exaggerated and bowel evacuations result. Belching is also common. The secretory activity of the intestinal tract tends to be enhanced, although this effect is naturally not as noticeable as with pilocarpine which stimulates the gland cells directly. The vasoconstriction which may accompany the action of physostigmine would act to reduce glandular secretion.

Skeletal Muscles. In normal persons, therapeutic amounts of physostigmine are without noticeable effect on skeletal muscle. Larger doses, however, cause generalized fibrillary twitchings, the muscles of the eyes, face, tongue, throat and extremities being affected earlier than those of the trunk and limbs. This action, more fully discussed under prostigmine, is not affected by atropine but can be blocked by curare (*see* Briscoe, 1936). After a large dose of physostigmine, the stimulation of muscles may be followed by a curariform depression (Morison and Rosenblueth, 1936). Completely denervated muscles no longer respond to physostigmine, but the action of injected acetylcholine on such muscles is intensified by physostigmine.

Other Actions of Physostigmine. Physostigmine tends to increase the *secretions* of the salivary, lacrimal, mucous and sweat glands but this action is less prominent than that of pilocarpine and muscarine. *Smooth muscles* receiving cholinergic innervation are stimulated, including those of the bronchi, ureters, urinary bladder, biliary ducts and spleen. The contraction of the spleen may cause a temporary increase in the circulating red and white blood corpuscles.

The *cardiovascular effects* of physostigmine are varied. Ordinary doses in man tend to slow the pulse and lower the blood pressure somewhat. This may be followed, especially with doses of two to four mgm, by a mild tachycardia and a rise in blood pressure of 10 to 20 mm of mercury. The ultimate effect of physostigmine on rate, rhythm and force of cardiac contraction and on blood pressure depends not only on the dose of drug and species of animal but also on the several factors outlined. In human beings, the nicotinic effects of physostigmine on cardiac sympathetic ganglia counteract to some degree the muscarinic actions, and thus the marked bradycardia and hypotension observed after muscarine and choline esters are not evident. Furthermore, physostigmine causes the *liberation of epinephrine* from the adrenal medulla and this produces vasoconstriction, tachycardia and a rise in blood pressure. Large doses of physostigmine, however, cause a significant fall in pulse rate and blood pressure.

The quantitative aspects of the *secretion of epinephrine* after the administration of physostigmine are quite interesting. Stewart and Rogoff (1921) found that the epinephrine content of the blood increased to as much as 15 times the normal after physostigmine. Edmunds and Smith (1932) showed that the epinephrine content of the adrenal glands in dogs receiving physostigmine intramuscularly fell within five hours to about one-third of the normal, and that repeated injections over a period of two or more days depleted the glands to about one-eighth of their normal content of hormone.

The effects of physostigmine, prostigmine and a number of closely related anticholinesterase chemicals have been studied for their actions on the *central nervous system* (Schweitzer and Wright, 1937, 1938, 1939; Kremer and coworkers, 1937; Miller and coworkers, 1940). These studies are of great academic interest for they attempt to extend the theory of chemical mediation of nerve impulses from the field of the peripheral autonomic nervous system to that of the brain and spinal cord (page 334). In brief, such investigations have shown that some physostigmine-like drugs tend to facilitate and others to inhibit central synaptic transmission of impulses, and the difference in the two groups of drugs has been related to their chemical structure. It is suggested that those anticholinesterase chemicals which are lipid-insoluble quaternary ammonium compounds preserve acetylcholine outside nerve cells and thus act as curare-like depressants; whereas those which are lipid-soluble tertiary ammonium bases preserve acetylcholine inside nerve cells and thus act as convulsive stimulants. The ultimate implications of these findings cannot be stated. As yet they have no therapeutic importance, and ordinary clinical doses of physostigmine have no significant action on the central nervous system of man. Doses which are larger than usual cause preliminary respiratory stimulation followed by depression, and toxic amounts are mainly depressant to the brain and cord.

Physostigmine Poisoning. The symptoms and signs of poisoning by physostigmine and prostigmine are sufficiently similar to allow a single description to suffice for both drugs. Poisoning from these alkaloids usually occurs accidentally in medical practice. Symptoms come on quickly after ingestion of the drug and soon reach their peak. The effects on the bowel are as a rule first to be noted and violent peristalsis, nausea, vomiting, colic, persistent purging and vomiting occur. The skeletal muscle phenomena consist of fibrillary twitchings all over the body, nystagmus and dysarthria. Restlessness and weakness are prominent. The pupils are pin-point in size and distant objects are blurred. Sweating, salivation and lacrimation may be marked. Dyspnea is present due to bronchiolar constriction and abundant pulmonary secretions. There is urinary urgency and difficulty in voiding. The skin is ashen-gray in color and bathed in a cold perspiration. The heart rate is rapid, the pulse weak and the blood pressure at shock level. Consciousness is not disturbed except for faintness and the fear of impending disaster. A fatal outcome is usually caused either by pulmonary edema or central respiratory paralysis. Death may occur within one-half to two hours after symptoms are first noted.

Treatment consists of hypodermic or intravenous administration of one to two mgm of atropine sulfate, dependent upon the urgency of the case. Atropine quickly counteracts the serious effects of physostigmine, namely, those on the lungs and circulation, but it does not influence the annoying but innocuous skeletal muscle twitchings. These subside as the drug is eliminated from the body.

Absorption, Fate and Excretion. Physostigmine is readily absorbed from the gastro-intestinal tract, subcutaneous tissues, and mucous membranes. The conjunctival instillation of solutions of the drug may result in systemic effects if measures are not used (pressure on inner canthus) to prevent absorption from the nasal mucosa. The alkaloid is partly destroyed in the body and the remainder is rather rapidly eliminated through the kidneys. In man, a one mgm hypodermic dose of physostigmine has exercised its action and is practically completely eliminated in two hours.

Therapeutic Uses

The clinical uses of physostigmine are quite limited. Although the drug is sometimes employed in conjunction with acetylcholine or mecholyl to enhance and prolong their effects, it is ordinarily not so prescribed. The chief applications of physostigmine are for its ocular and intestinal actions, and for myasthenia gravis.

Uses in Ophthalmology. Physostigmine is used in *glaucoma* to reduce intraocular pressure. Although in very acute attacks solutions as strong as one to two per cent have been employed, it is considered safer by some to use much weaker solutions (0.02 per cent) for chronic medication. Lamellae containing the drug may also be employed. In alternation with atropine, physostigmine solutions (0.1 to 1.0 per cent) may be helpful in breaking adhesions between the iris and lens. The drug may be given after a mydriatic to bring the pupil back to normal size and lessen the danger of increased intraocular tension. It is also prescribed in treating marginal corneal ulcers, an empirical use not well understood. Watery solutions of physostigmine may be irritating and cause conjunctivitis. To avoid irritation, small amounts of cocaine may be incorporated in the solution or the free alkaloidal base may be administered in an oil.

Intestinal Uses. In conditions of gastro-intestinal atony, such as paralytic ileus following anesthesia and operations, or the distention accompanying certain acute infections or toxic processes, physostigmine may be employed to restore bowel activity and assist in the evacuation of gas. A hypodermic dose of one to two mgm may be given, or one mgm of physostigmine may be combined with one-half to one cc of solution of posterior pituitary. Prostigmine is preferred to physostigmine for use in intestinal ileus by some clinicians. Acetyl-beta-methylcholine is similarly employed.

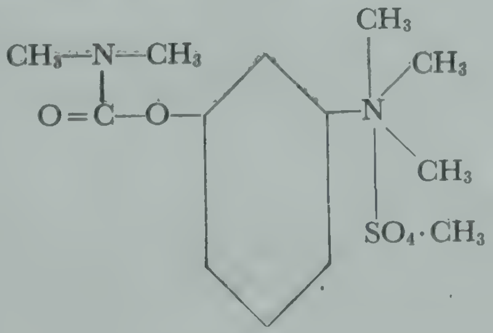
Martin and Weiss (1925) have suggested that much of the disappointment in the use of physostigmine in abdominal distention is due to two reasons—the administration of doses which are too small and the failure to distinguish between toxic and non-toxic cases. They find the average effective amount of physostigmine to be 3.0 to 4.0 mgm intramuscularly. This dose is safe if the patient is carefully observed, but should not be employed until simpler methods such as gastric or colonic irrigation, enemas and turpentine stupes have failed. Non-toxic cases (laparotomy, surgical shock, etc.) respond well but toxic cases (peritonitis, general toxemia, etc.) respond poorly or not at all.

Myasthenia Gravis. The use of physostigmine in myasthenia gravis is discussed under prostigmine.

PROSTIGMINE

Prostigmine is a synthetic alkaloid belonging to the physostigmine group of drugs. It is not to be confused with *geneserine,* an alkaloid found in the Calabar bean with physostigmine and sometimes referred to as prostigmine. Geneserine has the same qualitative actions as physostigmine but is only one-tenth as active (Heathcote, 1932). Prostigmine was introduced into therapeutics in 1931 for its stimulant action on the intestinal tract. Four years later it was found to be effective in the symptomatic therapy of myasthenia gravis.

Chemistry and Preparations. Prostigmine is available only in the form of its methylsulfate or bromide salt. The structural formula of prostigmine methylsulfate (dimethylcarbamic ester of 3-hydroxy-phenyl-trimethyl-ammonium methylsulfate) is as follows:



Prostigmine Methylsulfate

The salts are white crystalline powders which are odorless, bitter, and freely soluble and stable in aqueous solution. *Prostigmine Bromide,* N.N.R., being comparatively nonhygroscopic, is marketed in tablet form for oral administration. These tablets each contain 15 mgm of drug. *Prostigmine Methylsulfate,* N.N.R., is marketed in aqueous solution in 1.0 cc ampules containing either a 1:2000 (0.5 mgm) or 1:4000 (0.25 mgm) solution of the drug.

Relationship Between Chemical Structure and Action. Prostigmine is less complex in structure than is physostigmine. The researches of Stedman and collaborators (1926, *et seq.*) established the fact that the anticholinesterase activity of physostigmine and a number of allied compounds depended upon a fundamental chemical structure. Stedman's investigations established the fact that the methylcarbamic ester group, CH_3NHCOO, was the essential feature determining the activity of physostigmine and that all the related compounds manifesting anticholinesterase potency were basically substituted phenylesters of monoalkylcarbamic acids, having the general structure: $RNHCOOC_6H_4R^1$, R being a methyl or ethyl group and R^1 a basic group such as $—N(CH_3)_2$ or $—CH_2N(CH_3)_2$.

These important findings were extended by Aeschlimann and Reinert (1931) who studied a large series of synthetic compounds in an attempt further to elucidate the relationship between the structure and action of the physostigmine group and to find, if possible, drugs which might be more stable and more useful than physostigmine itself. One of the chemicals which these authors studied was prostigmine, which they found approximately as effective as physostigmine in producing miosis in cats and intestinal stimulation in rabbits.

Mechanism of Action. The mechanism of action of prostigmine, so far as is known at present, is similar to that of physostigmine—that is, it exerts its pharmacological effects by virtue of inhibiting the esterase which hydrolyzes and inactivates acetylcholine. No convincing evidence has yet been presented to prove that the highly selective actions of prostigmine are due to a *direct* effect of the drug on structures innervated by cholinergic nerves.

Pharmacological Actions. These need not be reviewed in detail because of their qualitative similarity to those of physostigmine. In man, prostigmine is said to be less active than physostigmine in causing miosis and spasm of accommodation. The same claim is made for its actions on the heart and blood pressure, but this important point needs confirmation.

On frog hearts at least, prostigmine has definitely weaker depressant actions than has physostigmine. In rabbits, doses of prostigmine necessary to lower the blood pressure are considerably larger than those which stimulate intestinal activity, but this also holds true for physostigmine. Prostigmine has the same effects as physostigmine on the intestine, urinary bladder and skeletal muscle, and is employed therapeutically for its actions on these structures. The drug further resembles physostigmine in possessing curariform effects on skeletal muscle when given in large doses. Therapeutic doses in man cause cutaneous vasodilatation, as indicated by a rise in temperature of the skin, but flushing does not occur (Perlow, 1939).

Atropine is the pharmacological antagonist to the muscarinic actions of prostigmine; curare, the antagonist to the skeletal muscle responses; nicotine, to the ganglionic actions.

Toxicology. The symptoms of prostigmine poisoning in man are similar to those seen with physostigmine (Goodman and Bruckner, 1937) and are described under the latter drug. The evidence available indicates that prostigmine has no wider margin of safety than has physostigmine. Indeed, the intravenous lethal dose of both drugs for mice is the same and toxicity studies in rabbits show that prostigmine given parenterally is from two to six times more lethal than physostigmine (Aeschlimann and Reinert, 1931). The use of prostigmine, therefore, demands the same caution and respect which attends the use of the older and more familiar drug physostigmine. In asthmatic patients, prostigmine may precipitate acute attacks of respiratory embarrassment and should therefore be employed with care.

Absorption, Fate and Excretion. Prostigmine is readily absorbed from the tissues after subcutaneous or intramuscular injection. It is also absorbed after oral administration, but much larger doses are needed by this route. Whereas the effective parenteral dose in man is from 0.5 to 2.0 mgm, the oral dose may be 30 mgm or more. Whether the drug is inactivated or destroyed in the intestinal tract or whether absorption is limited is not known. The large oral doses of prostigmine, such as are necessary in the therapy of myasthenia gravis, may prove toxic if intestinal absorption is enhanced for any reason. The exact fate of prostigmine in the organism is unknown. There is presumptive evidence that it is excreted in the urine.

Therapeutic Uses. Prostigmine is employed in therapeutics for its actions on the bowel, urinary bladder and skeletal muscle.

Intestinal Ileus. Prostigmine has been used in a manner similar to physostigmine for the relief of abdominal distention due to a variety of causes. The usual subcutaneous or intramuscular dose for postoperative intestinal ileus is 0.5 to 1.0 mgm of the methylsulfate salt. Peristaltic activity commences in from 10 to 30 minutes. A rectal tube should be inserted to facilitate the expulsion of gas. It may be necessary to assist evacuation with a small low enema.

The drug has also been employed in the prevention of postoperative intestinal atony, small doses (0.25 mgm) being given hypodermically soon after the operation and continued every four to six hours for two or three days. These small doses maintain normal intestinal tone without causing hyperperistalsis. The prophylactic administration of prostigmine is sometimes started before operation, but whether this is advisable as a routine procedure is doubtful. (*See* Harger and Wilkey, 1938; Marden and Williamson, 1939.)

Whether prostigmine is more valuable than physostigmine in paralytic ileus is a moot question. It is claimed by some that fewer side-actions (miosis, fall in blood pressure, bradycardia, bronchospasm, etc.) are noted after prostigmine.

Atony of the Urinary Bladder. Prostigmine has been employed for the prevention and treatment of atony of the detrusor muscle of the urinary bladder. The drug is used in the same dose and manner as in the management of intestinal ileus (Marden and Williamson, 1939).

Myasthenia Gravis. It was pointed out that myasthenia gravis may be due to a disturbance in the transmission of cholinergic nerve impulses to voluntary muscles, and the possible causes of the disorder were hypothecated (page 342). Regardless of the exact etiology of the disease, prostigmine and physostigmine, by inactivating cholinesterase, tend to increase the amount of acetylcholine at spinal motor nerve endings, and probably by this mechanism provide amelioration of symptoms.

In 1934, Dr. Mary Walker employed physostigmine in myasthenia gravis with beneficial results. She was prompted to do this because of the similarity of the muscular weakness in myasthenia to that noted in mild curare poisoning. In the following year, she found that better clinical results were obtained with prostigmine (Walker, 1935). Numerous clinical reports have confirmed these original findings. Why prostigmine is superior to physostigmine in myasthenia gravis is not known.

The exact mechanism by which prostigmine is of benefit in myasthenia gravis is not understood. Patients with this disease do not, as a rule, show abnormal values for *serum cholinesterase* (Lucas and coworkers, 1935; McGeorge, 1937; Hall and Lucas, 1937; Milhorat, 1938); but little is known concerning the cholinesterase activity of their skeletal muscles. It has been abundantly shown, however, that accompanying the improvement from the administration of prostigmine, there occurs a fall in serum cholinesterase activity. A similar fall occurs in the activity of skeletal muscle cholinesterase (Goodman, Carlson and Gilman, 1939). After the hypodermic administration of two or three mgm of prostigmine the serum cholinesterase activity is reduced from one-third to one-half of the resting level, with gradual restoration during a four to five hour period, toward the end of which the myasthenic symptoms return. The patient feels strong only during the period of drug-induced depression of the cholinesterase activity. The correlation between the improvement in symptomatology and the reduction in serum and muscle cholinesterase activity induced by prostigmine is illustrated in Figure 38.

The important relationship existing between potassium and cholinergic nerve transmission is discussed elsewhere (pages 341, 596) but it is interesting to observe at this point that Cumings (1939) has reported high values for potassium in the skeletal muscles of patients with myasthenia gravis. After the administration of prostigmine, the potassium content of the muscles decreased toward normal concurrently with the return of normal muscle power. The correlation of these findings with the anticholinesterasic property of prostigmine and with the cholinergic transmission of nerve impulses to skeletal muscles is not as yet clear.

Clinical Results. Striking improvement may appear in from 10 to 30 minutes after the parenteral injection of prostigmine, or within an hour or two after oral administration. The patient is benefited for from four to six hours and the drug is therefore repeated three or four times daily. Muscle power returns and a completely helpless individual can be transformed almost to normal. Ptosis, ophthalmoparesis, dyspnea, dysphagia, dysarthria and weakness of the neck, limbs and trunk are greatly or completely relieved. Patients can often return from invalidism to an ambulatory or even economically useful existence by the judicious use of prostigmine (Viets and Schwab, 1939).

In some patients, especially those who are severely ill, benefit may be temporary and can be sustained only by the use of larger and larger doses of the drug. These individuals require a progressively greater reduction in their (serum) esterase activity in order to maintain clinical improvement (Milhorat, 1938). The time may come when the drug is no longer capable of affording relief and a rapid downhill course then leads to death despite continued use of prostigmine. It is suggested that, if possible, other drugs (ephedrine, glycine, guanidine, choline esters) be substituted for prostigmine in such patients in an attempt to restore susceptibility to prostigmine. Some clinicians prefer to use prostigmine only as a supplement to ephedrine or glycine therapy. Others reserve it for use in emergencies. Nevertheless, the drug is an extremely valuable addition to the agents available in the therapy of myasthenia gravis. The combined use of ephedrine and prostigmine, in particular, comprises a valuable form of treatment, the two drugs apparently potentiating each other. The results obtained with prostigmine in combination with ephedrine, aminoacetic acid, guanidine, and certain other agents have been reviewed especially by Viets and Schwab (1939) and by Schlezinger (1940).

Dose. The initial hypodermic dose of prostigmine in myasthenia gravis is 0.5 mgm. This is then increased if necessary. The optimal dose is repeated two to four times daily. Because therapy is chronic, oral administration is much to be desired. This route is evidently safe, despite the large amounts of prostigmine

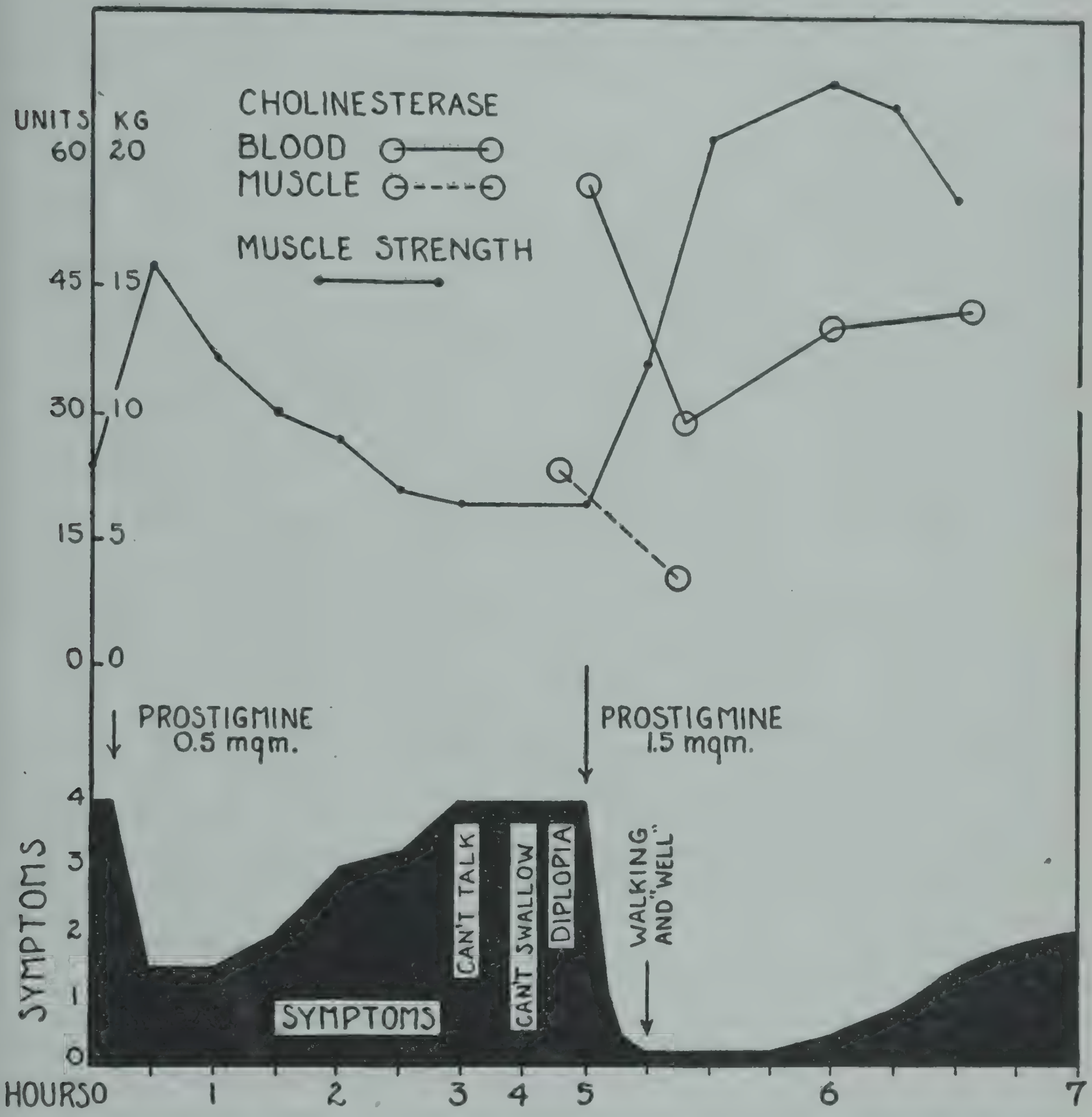


Figure 38. *The effect of prostigmine in myasthenia gravis.*

The severity of symptoms is shown on an arbitrary scale. Muscle strength was measured by a double hand-dynamometer. Pectoral muscle biopsies and blood samples were taken at the height of symptoms, and at the peak of improvement following the subcutaneous administration of prostigmine. One unit of cholinesterase is the amount which liberates 0.01 cc of 0.01 N acetic acid in five minutes from a solution containing 100 mgm of acetylcholine bromide in 25 cc.

The patient was a white male, aged 33, who had had myasthenia gravis for 16 years. Prostigmine in doses of 0.5 mgm caused only moderate relief of symptoms lasting less than two hours. Muscle strength decreased and symptoms progressed until the patient was absolutely helpless. After 1.5 mgm of prostigmine were injected, the patient was able to walk within 15 minutes, and said he felt "tops." Coincident with the symptomatic improvement there occurred a marked fall in the cholinesterase activity of the blood serum and muscle. Inhibition by prostigmine of the enzyme in skeletal muscle probably accounts for the increase in muscle strength. As symptoms returned, the cholinesterase activity of the blood increased. Note the change in time scale. (Goodman, Carlson and Gilman, 1939.)

necessary, provided atropine (0.3 mgm) or tincture of belladonna (0.6 to 1.5 cc) is used three times daily to prevent any of the untoward reactions on the intestinal, respiratory and cardiovascular systems. This prophylactic use of belladonna does not in the least impair the action of prostigmine on the skeletal muscles because atropine blocks only the muscarinic actions of parasympathomimetic drugs. The oral dose of prostigmine is from 15 to 30 mgm three times daily. Each patient must be studied carefully in order to find the optimal dosage, and frequent changes may be necessary in the dose schedule. Patients in relapse must be seen often.

Diagnostic Use of Prostigmine. Prostigmine has been tried in other myopathies characterized by muscular weakness, but the results have not been encouraging. These disorders include progressive muscular dystrophy, hypertrophic muscular dystrophy, amyotrophic lateral sclerosis, progressive ophthalmoplegia, progressive bulbar palsy, marked weakness following severe infections, etc. Indeed, so specific is the action of the drug in myasthenia gravis that prostigmine can be employed as a diagnostic test in doubtful cases (Viets and Schwab, 1935; Gammon and Scheie, 1937; Harvey and Whitehill, 1937), especially when used in conjunction with ergographic or electromyographic recordings. Quinine, which intensifies the symptoms of myasthenia gravis, may be given beforehand to those patients in whom symptoms are not well developed, and prostigmine may then be employed to improve the muscular weakness exaggerated by the quinine (page 908).

Other Drugs Useful in Myasthenia Gravis. In addition to prostigmine, several other pharmacotherapeutic agents are available for the symptomatic therapy of myasthenia gravis, including *ephedrine, benzedrine,* and the *choline esters* (*see* Index). *Glycine,* N.N.R., (glycocoll, aminoacetic acid), CH_2NH_2COOH, has also been observed to be of benefit in certain cases for varying periods of time (*see* Boothby, 1934; Report of the Council, 1935). It is a light, white, odorless, crystalline powder, possessing a sweetish taste and freely soluble in water. The dose varies from 15 to 30 grams per day, given in divided portions. The exact mechanism by which glycine exerts its effect on muscle contraction is not understood, despite the considerable information available from biochemical experimentation concerning the influence of aminoacetic acid on creatine-creatinine metabolism in health and in muscular dystrophies. *Guanidine,* $NH{:}C(NH_2)_2$, in the form of its *hydrochloride* or *carbonate* salt, has had a limited clinical trial in the treatment of myasthenia gravis. In some patients, it apparently is capable of causing symptomatic improvement alone or in combination with other drugs used in the syndrome, especially prostigmine (Minot, Dodd and Riven, 1939; Viets and Schwab, 1939). The initial dose is 10 mgm per kg taken orally in gelatin capsules, and the dose is increased as required. The total daily dose may vary from 10 to 35 mgm per kg, given in three or four divided portions. If necessary, the intravenous route may be employed, a two per cent solution of guanidine hydrochloride in isotonic sodium chloride being used. The subcutaneous and intramuscular routes cannot be utilized because of local irritation from the drug. The mechanism of action of guanidine in myasthenia gravis is unknown. Minot (1939) has shown that the chemical does not inhibit the activity of serum cholinesterase, and she and her coworkers (1939) are inclined to favor the view that guanidine increases the sensitivity of skeletal muscle to acetylcholine. The close chemical relationship between glycine, creatine and guanidine is evident, however, and suggests that glycine and guanidine may possibly exert their actions primarily by an effect on muscle metabolism. Patients with myasthenia gravis are evidently more tolerant of the chemical than are normal individuals who may experience symptoms of hyperguanidinemia, including nervousness, hyperperistalsis and diarrhea. *Potassium salts,* such as the *chloride* or *citrate,* have also produced improvement in the disease, and the rôle of potassium in the chemical mediation of nerve impulses may be the basis of the action of this cation in myasthenia gravis. Certain other muscular dystrophies, notably familial periodic paralysis, are also aided by potassium.

The aforementioned drugs may be employed in various combinations. Better results, for example, are often obtained when glycine and ephedrine or prostigmine and ephedrine are administered than when a single drug is used.

Other Uses. Prostigmine has had a preliminary but promising trial in *atrophic rhinitis.* Soskin and Bernheimer (1939) treated 14 patients suffering from advanced atrophic rhinitis with *ozena,* 0.25 cc of a 1:2000 solution of prostigmine methylsulfate being sprayed in each nostril four times daily. No untoward effects were noted. The degree of permanence of the beneficial results has not yet been established. Prostigmine has been shown to increase muscle tone in normal persons (McGeorge, 1937) and to cause a pronounced exacerbation of symptoms in *myotonia congenita* (Russell and Stedman, 1936; Kennedy and Wolf, 1937), a disease benefited by quinine. The drug has been employed in cases of *delayed menstruation* to induce the menstrual flow and as a *diagnostic test of early pregnancy.* Its value for these purposes requires confirmation. Prostigmine has also been administered orally for the treatment of *peripheral vascular disturbances* characterized by vasospasm or occlusive disease (Perlow, 1940). Prostigmine likewise has been used in a number of syndromes and diseases other than those mentioned but without definite benefit.

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CHAPTER 22

DRUGS STIMULATING STRUCTURES INNERVATED BY CHOLINERGIC NERVES (PARASYMPATHOMIMETIC DRUGS)

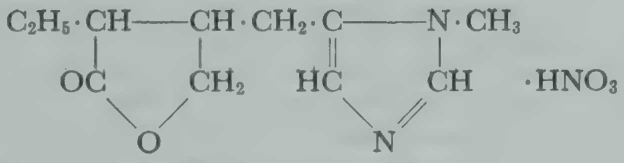
III. PILOCARPINE, ARECOLINE AND MUSCARINE

PILOCARPINE

Historical. Pilocarpine is the chief alkaloid obtained from the leaflets of South American shrubs known as *Pilocarpus jaborandi* and *Pilocarpus microphyllus.*

. The alkaloid was isolated by Hardy in 1871. Although it was long known by the natives that the chewing of leaves of *Pilocarpus* plants caused salivation, the first experiments were apparently performed in 1874 by a Brazilian physician named Coutinhou. Using an extract of pilocarpine, he showed that the drug also caused marked sweating. In 1876, the actions of pilocarpine on the pupil as well as on the sweat and salivary glands were described by Weber. Numerous other contributions to the pharmacology of this alkaloid rapidly followed.

Chemistry and Preparations. Pilocarpine base is a viscid, colorless oil which readily forms salts with mineral acids. Solutions of these salts are dextrorotatory. The hydrochloride and nitrate salts are available. *Pilocarpine Hydrochloride,* N.F., consists of very hygroscopic, colorless, translucent crystals. *Pilocarpine Nitrate,* U.S.P., B.P., consists of shining, colorless crystals, highly soluble in water and slightly bitter to the taste. The average adult oral dose of pilocarpine nitrate is five mgm. The structural formula of pilocarpine nitrate is as follows:



Pilocarpine Nitrate

Mechanism of Action. The autonomic responses to pilocarpine are due to a highly selective action of the alkaloid on cells innervated by postganglionic cholinergic fibers. This action is a direct one on the reactive substance and occurs after nerve section and complete nerve degeneration. Pilocarpine thus acts by an entirely different mechanism than does physostigmine. Pilocarpine is similar to muscarine and arecoline in its pharmacological properties and exhibits most of the muscarinic effects of acetylcholine. The nicotinic properties of acetylcholine are not manifest in the actions of pilocarpine. Atropine is the pharmacological antagonist to pilocarpine and counteracts or prevents all of the autonomic responses to the latter drug.

Pharmacological Properties

Pilocarpine stimulates the involuntary smooth muscle and gland cells innervated by postganglionic cholinergic nerves. Particularly responsive to pilocarpine are the sweat and salivary glands. The other actions of the alkaloid in the body, with the exception of miosis, are not therapeutically important and constitute undesirable side-effects. For this reason, pilocarpine lacks the wide range of usefulness enjoyed by the esters of choline. The alkaloid has few clinical uses and is perhaps not indispensable in medicine. It is unnecessary, therefore, to discuss in detail the responses of all autonomic structures to this drug.

Sweat Glands. For many years, the action of pilocarpine on sweat glands was viewed as an anomaly because the glands are devoid of parasympathetic innervation. It is now known that the nerve fibers supplying sweat glands, although anatomically sympathetic, are in reality cholinergic and this type of innervation explains their responses both to pilocarpine and atropine (page 331). Pilocarpine (10 to 15 mgm) causes marked diaphoresis in man when administered hypodermically and two to three liters of sweat may be secreted. This sweat contains not only the electrolytes of the extracellular fluid but also nitrogen in the form of urea. If the non-protein nitrogen of the blood is elevated, as in nephritis, the enhanced sweating caused by pilocarpine may allow for considerable extrarenal elimination of urea, amounting at times to as much as eight grams of nitrogen. Diaphoretic doses of pilocarpine, however, may also produce unpleasant side-actions such as hiccoughing, salivation, nausea, vomiting, weakness and occasionally collapse.

The *secretion of sweat* in man in response to pilocarpine and the esters of choline has been the subject of investigation by a number of workers, especially Wilson (1934) and List and Peet (1938). The diaphoretic response to these drugs is essentially similar, and has more pharmacological than clinical significance. The sweating produced by drugs is of limited diagnostic value in demonstrating the nature of peripheral nerve lesions, and it is much less pronounced in the lower extremities than in the rest of the body. It is claimed by some that the sweating reaction to drugs in man differs from that in animals, inasmuch as diaphoresis occurs in animals in cutaneous areas in which degeneration of nerves to sweat glands has taken place. This difference is denied by Wilson who found that after degeneration of the secretory ("sympathetic") nerves to sweat glands in human subjects, an excessive response occurred to pilocarpine (10 to 15 mgm) injected subcutaneously. In contrast, sensory nerve degeneration was usually associated with a diminished secretory response to pilocarpine, probably due to alterations in the cutaneous vascular bed. Wilson also demonstrated that intradermal injection of solutions of pilocarpine caused a "triple response," similar to that caused by histamine (page 561), and local sweating. Atropine injected into the same area caused prompt cessation of the sweating. Wilson concluded that pilocarpine acts directly on sweat glands in man and also that it dilates the minute vessels of the skin. Similar results were obtained with acetylcholine. The intervention of secretory nerve endings evidently is not essential for the sweating response to these drugs.

List and Peet likewise investigated the sweating response in man to subcutaneously administered pilocarpine (10 to 16 mgm) and acetyl-β-methylcholine (12 to 25 mgm). They found that thermoregulatory sweating disappears completely after various forms of sympathectomy in which the postganglionic cholinergic fibers to the glands are interrupted, and that the heat test of sweating is a simple and accurate clinical method to determine the extent and site of lesions in the sympathetic nervous system. Pilocarpine and mecholyl still induce sweating after sympathectomy, but no longer do so after degeneration of mixed peripheral nerves or purely sensory cutaneous nerves. Heat sweating also disappears after section and degeneration of peripheral cutaneous nerves. When the somatic nerve is blocked by infiltration with procaine, however, only heat and not drug-induced sweating disappears.

The presence in peripheral somatic nerves of cholinergic fibers to sweat glands other than those of sympathetic origin appears likely; but it is not at all clear why complete anhidrosis should follow interruption of these nerves by resection and not after infiltration with procaine. List and Peet are inclined to interpret their findings as indicating a direct action of pilocarpine and mecholyl on nerve endings rather than on sweat glands. Such a conclusion is certainly not in harmony with the bulk of evidence concerning the action of drugs on autonomically innervated structures. Present concepts hold that autonomic drugs act directly on effector cells and not on nerve endings (page 336), act regardless of the integrity of the innervation, and indeed may show enhanced potency after complete denervation of the effector organs (page 342). In this connection, an additional observation of Wilson is pertinent. The sweating which followed the intracutaneous injection of acetylcholine could be prolonged by the prior local injection of eserine, which prevented the hydrolytic destruction of acetylcholine by cholinesterase in the skin. No such potentiation by eserine of the sweating response to intradermally administered pilocarpine was demonstrable, thus indicating that pilocarpine did not stimulate nerve endings to release acetylcholine. The anomalous behavior of drug-induced sweating responses in man with various types of peripheral nerve injury or section awaits further elucidation.

Other Glands. Many glands which receive postganglionic cholinergic fibers and elaborate external secretions are stimulated in varying degrees by pilocarpine. These include the salivary, lacrimal, gastric, pancreatic and intestinal glands, and the mucous cells of the respiratory tract. Copius *salivation* follows the administration of therapeutic amounts of pilocarpine. In man, as much as 350 cc may be secreted over a period of two hours in response to 10 mgm of the drug. Normal saliva is one of the few hypotonic fluids that the body elaborates and is also unique in containing a larger amount of potassium than does the extracellular fluid from which it is derived. After pilocarpine, the saliva tends to approach in composition that of an ultrafiltrate of the serum.

The *gastric glands* are stimulated to secrete a juice rich in acid but especially abundant in pepsin and mucin, simulating in this respect the effects of vagal impulses. Only certain choline esters exceed pilocarpine in this ability to stimulate the secretion of pepsin. Pilocarpine is inferior to histamine in causing secretion of hydrochloric acid. The effects of pilocarpine on *pancreatic* and *intestinal* secretions are not prominent. The glands of the *respiratory* tract are activated by the alkaloid, large doses of which can produce sufficient bronchiolar secretion to cause pulmonary edema.

Eye. Pilocarpine nitrate, when applied locally to the eye, causes pupillary constriction, spasm of accommodation and a transitory rise in intraocular pressure, followed by a more persistent fall. Miosis lasts from several hours to a day, but fixation of the lens for near vision disappears in about two hours.

Other Actions. Theoretically, all structures receiving cholinergic innervation are stimulated by pilocarpine but this generalization does not hold true for the heart. Slowing of the heart is fleeting and uncertain. Cardiac rate may actually be increased in man by therapeutic doses of the drug (Wilson, 1934). Peripheral vasodilatation occurs after pilocarpine, but is less marked than the response to acetylcholine and muscarine. The *blood pressure* therefore does not fall, and in fact it may rise somewhat, especially the systolic level (Blomberg and Rönnell, 1930; Wilson, 1934). These apparently anomalous reactions of the cardiovascular system to pilocarpine are not well understood.

The alkaloid stimulates the *smooth muscles* of the *intestinal tract*, thus increasing tone and motility, and large doses cause marked spasm and tenesmus.

The tone and motility of the *ureters, urinary bladder, gall bladder* and *biliary ducts* are also enhanced by pilocarpine. The *bronchioles* are constricted by pilocarpine and this action, in conjunction with the enhanced secretory activity of bronchial glands, results in a condition simulating bronchial asthma. The *spleen* contracts due to stimulation of its capsular musculature. This is probably the basis for the *leukocytosis* sometimes noted after the drug.

When injected into the *cerebral ventricles* of man, small doses of pilocarpine (2.5 mgm) cause widespread vasodilatation, sweating, vomiting and decrease in body temperature (Cushing, 1932). Similar effects have been noted from intraventricular instillation of posterior pituitary substance, and the phenomenon has been interpreted as a central autonomic stimulation, predominantly parasympathetic in character. These central responses are not noted after oral or hypodermic administration of pilocarpine. Other actions of the alkaloid on the nervous system are not prominent, but large doses cause central depression.

Pilocarpine Poisoning. Poisoning due to pilocarpine is rare. The symptoms simulate those of muscarine to which the drug is pharmacologically closely allied. Marked salivation, lacrimation and sweating occur. Nausea, vomiting, tenesmus and diarrhea are prominent. Vision for far objects is blurred and the pupils are greatly constricted. Breathing may be difficult due to bronchiolar spasm, and edema of the lungs from excessive secretion may prove fatal. The pulse rate may be fast or slow and the blood pressure falls. Muscular weakness, tremor, vertigo, confusion, marked depression and ultimately collapse ensue. Death is usually due either to pulmonary edema or central respiratory failure, and may occur within a few hours. The *fatal dose* is unknown but 100 mgm may be viewed as a dangerous amount. *Treatment* consists of administration of atropine, and symptomatic measures designed to support the respiration and circulation and to counteract edema of the lungs.

Fate and Excretion. Pilocarpine is partly destroyed in the body but the greater part is excreted in the urine in combined form.

Therapeutic Uses. *Eye.* Pilocarpine is used to produce miosis. It can be administered as a 0.5 to 3.0 per cent solution, in the form of an ointment or in gelatin lamellae. The miotic action of pilocarpine may be useful in overcoming the mydriasis of atropine, or in glaucomatous conditions. Alternated with mydriatics, pilocarpine may be employed to break adhesions between the iris and the lens.

Diaphoresis. The practice of using pilocarpine to cause sweating in order to rid the body of edema fluid, exudates or nitrogenous material is now practically obsolete. Severe side-effects accompany the use of effective diaphoretic doses. If sweating or fluid elimination is desired, safer and less strenuous methods are available. Pilocarpine, as was stated previously, has been employed in investigating disturbances in the sweating mechanism as a result of peripheral nerve lesions, the moisture being detected either by the red color imparted to an alcoholic solution of cobalt blue previously painted on the skin or by the iodine color reaction test of Minor (1927). Small doses of the alkaloid have been used to alleviate generalized *itching,* as in portal cirrhosis. The mechanism of relief may be related to sweating or to slight changes in the cutaneous circulation.

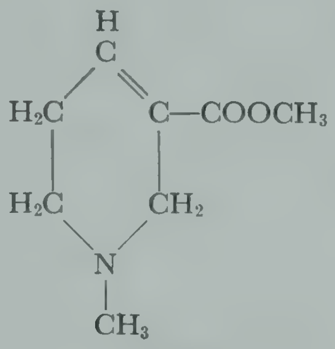
Salivation. Pilocarpine may be given to induce salivation when xerostomia is an unpleasant symptom, as in atropine overdosage or botulism.

Miscellaneous Uses. Pilocarpine is occasionally incorporated in medicines for use in unproductive coughs, where it may act as an *expectorant* by virtue of its stimulation of bronchial glands. The drug has gained a false reputation as a hair restorer, based on its action on sebaceous glands, and it is thus incorporated in certain hair tonic nostrums. No beneficial effect can reasonably be expected after local cutaneous application of the alkaloid. Pilocarpine is useful to a certain degree in counteracting the peripheral autonomic effects in cases of *atropine poisoning,* but the serious features of the intoxication, which are due to the central actions of atropine, are unaffected.

ARECOLINE

Arecoline is the chief alkaloid of areca nuts, the seeds of *Areca catechu.* This nut is also known as the *betel nut* because it has been consumed by the natives of the East Indies from early times in a masticatory mixture known as *betel* and composed of the areca nut, shell lime and the leaves of *Piper betle,* a climbing species of pepper. The mixture stains the teeth black. The use of betel nut as a taenicide was known to the Chinese as early as the 6th century, and the nut is still employed for that purpose in China (Hsiao-Liang, 1936).

Chemistry and Preparations. Arecoline is a reduced pyridine derivative with the following relatively simple structure:



Arecoline

There is no apparent chemical basis for the similarity in actions of arecoline, pilocarpine and muscarine. *Areca* (Areca Nut, Betel Nut), N.F., is the dried ripe seed of the plant. The N.F. alkaloidal salt is *Arecoline Hydrobromide,* a white, crystalline, water-soluble powder.

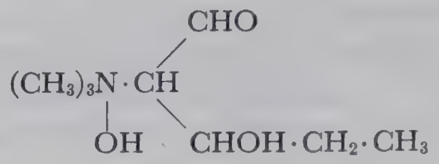
Actions. Arecoline shares many of the pharmacological properties of pilocarpine and muscarine in that it stimulates, by a direct action, those smooth muscles and gland cells innervated by postganglionic cholinergic nerve fibers. It is qualitatively similar in action to pilocarpine in all respects but is more powerful.

Uses. Although arecoline is official in certain pharmacopeias and is employed as a diaphoretic, sialogogue and taenicide in some parts of the world, it is not prescribed in modern therapeutics. Arecoline is occasionally utilized in veterinary medicine as a vermifuge, the expulsion of worms being accomplished by the marked stimulation of peristalsis which the drug produces. The average dose for a horse is 30 mgm; for a dog, 1.5 mgm per kg. The use of betel nut as a taenicide by the Chinese has been mentioned. The charcoal obtained from areca is very hard and is sometimes incorporated in dentifrices.

MUSCARINE

Muscarine is a drug which, though not employed clinically, is of considerable historical and experimental significance. The poisonous effects of certain species of mushrooms were known for a long time but it was not until Schmiedeberg isolated the alkaloid muscarine from *Amanita muscaria* that the properties of the drug could be systematically investigated. Schmiedeberg and Koppe made the first careful pharmacological study of muscarine in 1869. The close resemblance between the responses to vagal stimulation and to muscarine led Dixon to postulate that a muscarine-like substance might be the chemical agent through which vagal impulses were mediated (page 324).

Chemistry. Muscarine is a quaternary ammonium base with the following structural formula (Kögl and associates, 1931):



Muscarine

Its close chemical relation to choline, another constituent of *Amanita muscaria*, and to the esters of choline can be seen by comparison with the formulas shown on page 351.

Actions. Muscarine, by a direct action, stimulates smooth muscles and gland cells innervated by postganglionic cholinergic nerves. Thus it shares the pharmacological properties of pilocarpine and arecoline, and particularly those of acetylcholine, because, like the last-named drug, it causes typical cardiac slowing and peripheral vasodilatation. So similar are the responses of the heart, smooth muscles and glands to muscarine and acetylcholine that the term "muscarinic" is employed to designate the action of acetylcholine on these structures, in distinction to the "nicotinic" action of acetylcholine on autonomic ganglia and skeletal muscles (page 339). Muscarine, however, can be shown to possess some nicotinic properties but these are not prominent. As might be predicted, the chief effects of muscarine in the mammalian organism are cardiac slowing, depression of blood pressure, vasodilatation, increased peristalsis, miosis, bronchial constriction, salivation and sweating. Small doses of atropine completely inhibit these responses to muscarine.

Uses. Muscarine has no therapeutic uses, and is mainly of laboratory interest as a pharmacological tool. It is rather difficult to obtain in pure form.

Mushroom Poisoning (Mycetismus)

Mushroom poisoning has been known for centuries. The Greek poet Euripides (5th century B.C.) is said to have lost his wife and three children from this cause. Mushrooms were employed by professional poisoners in ancient times. The increased incidence of mycetismus during the early 1930's has been attributed to the eating of wild mushrooms because of the economic depression.

The *Amanita* genus of mushroom is responsible for nearly all cases of mushroom poisoning in the United States, and the delicious but deadly *phalloides* species causes over 90 per cent of the fatalities. Occasionally, *Amanita muscaria* may cause death. These two species are common in North America. Poisonous mushrooms can be differentiated from edible ones only by their botanical characteristics and not by such fallacious lay tests as the tarnishing of silver coins placed in the cooking utensil. Rarely does the physician have an opportunity to identify the type of plant responsible for the intoxication and he must therefore depend on the history and symptoms in order to make his diagnosis. Two types of mushroom poisoning occur in the United States, the *rapid* and the *delayed*.

The *rapid* type (mycetismus nervosus) is caused by *Amanita muscaria* which contains the alkaloid muscarine. Symptoms are due especially to muscarine and occur within a few minutes to an hour or two after ingestion of the fungus. They are similar to those described under pilocarpine poisoning. There is marked lacrimation, salivation, sweating, miosis, dyspnea, severe abdominal pain, frequent watery and painful bowel evacuations, cardiovascular collapse, vertigo, weakness, confusion, coma and occasionally convulsions. In fatal cases, death occurs within a few hours. Atropine provides a specific antidote and the prognosis is good even in severe cases if this form of intoxication is recognized and atropine is administered.

The *delayed* form (mycetismus choleriformis) is due to *Amanita phalloides* which probably contains several toxins, as yet not completely identified. Symptoms occur in from six to 15 hours after ingestion of the fungus and are heralded by the sudden onset of severe abdominal pains, nausea, vomiting and diarrhea. The stools and vomitus are often blood-streaked. Dehydration is marked and thirst is extreme. The course of intoxication is prolonged. Jaundice develops in two or three days secondary to severe degenerative changes and fatty infiltration of the liver. Acute yellow atrophy of the liver may also occur. The kidney parenchyma is similarly involved and oliguria or anuria ensues. Cyanosis, low blood pressure and feeble heart action are the result of extensive capillary damage and a direct toxic action on cardiac muscle. Increasing prostration terminates in coma, which is probably due in large part to the direct cellular damage in the central nervous system produced by the *Amanita phalloides* toxin. The prognosis is grave. The mortality rate is at least 50 per cent, and often approaches 100 per cent. Death occurs in from five to eight days after the ingestion of the mushrooms. Treatment is purely symptomatic and supportive, and includes prolonged rest in bed, opiates for pain, and shock therapy when indicated. The value of antitoxic sera in cases of poisoning by *Amanita phalloides* is unproved.

The interested reader is referred for the classification and details of mushroom poisoning especially to Ford (1923) and Vander Veer and Farley (1935). The botanical characteristics of these fungi, which are not germane to the present discussion, may be found in botanical and pharmacognosy texts.

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CHAPTER 23

DRUGS STIMULATING STRUCTURES INNERVATED BY ADRENERGIC NERVES

(SYMPATHOMIMETIC DRUGS)

I. EPINEPHRINE

A large number of sympathomimetic drugs are known and several of these are widely used in therapeutics. Although they resemble each other in many respects, each possesses certain unique properties which are often of value for specific clinical purposes. In general, the sympathomimetic amines elicit responses in the body which simulate those resulting from stimulation of adrenergic nerves, but the details and intensities of these responses often differ widely. In addition, several of the compounds produce profound effects on the central nervous system. Drugs in this category thus have a variety of clinical uses and it is therefore necessary for the physician not only to understand the general pharmacology of the group as a whole but also the manner in which the various members differ. In the following discussion, particular attention will be paid to the two older members of the group, epinephrine and ephedrine, and the many similarities and differences between these two compounds will serve as a background for the description of the agents which have subsequently been introduced.

EPINEPHRINE

Source and History. Epinephrine, the active principle of the adrenal medulla, was the first hormone to be isolated in crystalline form. Curiously, epinephrine is also found, along with substances resembling cardiac glycosides, in the secretions of glands of toads, and the parotid glands of a single Jamaican toad (*Bufo marinus*) contains more than four times the amount of hormone present in a pair of human suprarenal glands. Epinephrine is closely related to the amino acid *tyrosine* which may be the precursor of the hormone in the animal body. Decarboxylation of tyrosine yields *tyramine,* a substance found in ergot and putrefying meat and formed from protein in the intestinal tract in the presence of bacteria. Tyramine resembles epinephrine in its sympathomimetic properties but is much weaker. The *in vitro* synthesis of an epinephrine-like substance from phenylethylamine, phenylalanine and tyramine, but not from tyrosine or methyl tyrosine has been demonstrated by Devine (1940) to occur in surviving tissue slices of the adrenal medulla (bullock).

In 1895, Oliver and Schäfer demonstrated the actions of extracts of the adrenal medulla on the cardiovascular system, marked rises in blood pressure occurring after intravenous injection of the extracts into animals. No such potent vasopressor substance was known at that time, and their experiments initiated intensive pharmacological investigations which soon resulted in the elucidation of the chemical structure of the active principle through the efforts of Abel (1897, 1899), von Fürth (1900), Takamine (1901), Aldrich (1905) and others. Epinephrine was then synthesized independently by Stolz (1904) and Dakin (1905), and its optical isomers separately by Flächer (1908). The history of the isolation and identification of epinephrine has been reviewed by Hartung (1931).

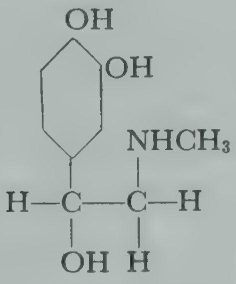
Barger and Dale (1910) examined a large series of related synthetic amines, defined the basic structural requirements for pharmacological activity and introduced the term "sympathomimetic" to describe the type of action manifested by the group as a whole. The details of their now classical contribution are included in the discussion of the relationship between chemical structure and pharmacological properties.

In the early 1920's, the investigations of Loewi and Cannon and their respective collaborators disclosed the importance of an epinephrine-like substance in the mediation of the excitatory state produced by nerve impulses at neuromuscular and neuroglandular junctions. The significance and details of these discoveries and the concept of sympathin E and sympathin I are presented in detail in Chapter 19.

Chemistry of Epinephrine and Related Compounds and the Relation of Chemical Structure to Pharmacological Activity. Shortly after the chemical structure of epinephrine was determined, studies of the pharmacological actions of chemically related compounds began to appear. Investigations of this nature have continued to the present and have resulted in the introduction of many valuable therapeutic agents.

The first extensive study on compounds chemically related to epinephrine was the classical investigation of Barger and Dale (1910). The conclusions drawn by them are still valid and their work formed the impetus not only for the study of compounds chemically related to epinephrine but stimulated interest in synthetic drugs in general. Some of the compounds which Barger and Dale investigated are only now becoming prominent. For these reasons a brief summary of their experiments is not only of historical but also of current interest.

Before considering the contributions of Barger and Dale, a study of the chemical structure of epinephrine is pertinent. Its structural formula is as follows:

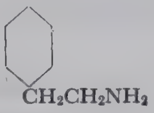
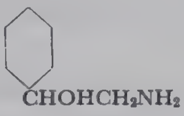
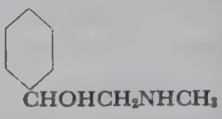
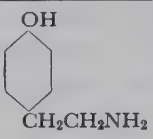
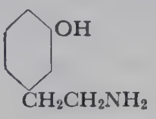
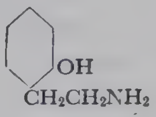
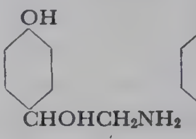
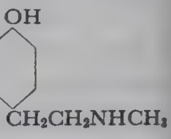
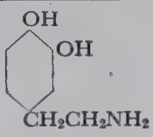
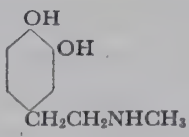
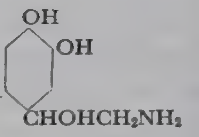

Epinephrine

The epinephrine molecule may be viewed as composed of two major constituents. The aromatic portion consists of dihydroxybenzene (catechol); the aliphatic, of alpha-hydroxy-beta-methylamino ethane. In the following discussion, the carbon atom attached to the benzene ring is designated as the *alpha* carbon.

Barger and Dale began their study with an investigation of simple aliphatic amines. They observed that amines of low molecular weight (I) had no sympathomimetic activity (Roman numerals refer to compounds listed in Table 20). When a four carbon atom structure was reached (II), however, definite activity appeared, reached its maximum with six carbon atoms (III) and then receded as the length of the aliphatic chain was further increased (IV). In the aliphatic series, substitution in the amino group resulted in a loss of activity and quaternary ammonium bases possessed an entirely different type of action which resembled that of curare. They then went on to study the effect of introducing a phenyl group into simple aliphatic amines. The presence of the aromatic ring increased activity and of this series phenylethylamine (V) was the most potent. Decreasing or increasing the number of carbon atoms on the aliphatic portion of the molecule resulted in a loss of activity. Furthermore, the presence of a hydroxy group on the alpha carbon (VI), or a methyl group on the nitrogen, or both (VII), failed to increase activity. Barger and Dale then studied the effect of adding one hydroxy group to the benzene ring. If the hydroxy group was placed para (VIII) or meta (IX) to the aliphatic chain, activity was increased three to five times, but ortho substitution (X) was without effect. As before, two carbon atoms before the nitrogen gave maximal activity. Also, as before, the presence of a hydroxy group on the alpha carbon atom (XI) or a methyl group on the nitrogen (XII) failed to affect pharmacological actions.

Table 20

SYMPATHOMIMETIC AMINES *

Aliphatic Amines	$CH_3CH_2NH_2$ I	$CH_3(CH_2)_3NH_2$ II	$CH_3(CH_2)_5NH_2$ III	$CH_3(CH_2)_6NHCH_3$ IV	
Phenyl Amines	 V	 VI	 VII		
Hydroxyphenyl Amines	 VIII	 IX	 X	 XI	 XII
Dihydroxyphenyl Amines	 XIII	 XIV	 XV		

* See text for explanation.

Barger and Dale then proceeded to a consideration of compounds possessing two hydroxy groups in the benzene ring. Only when the hydroxy groups were in the para and meta positions (XIII) was activity enhanced. In this series, however, the insertion of a methyl group into the primary amine (XIV) further increased activity five to 10 times. Ethyl amines and propyl amines were less active than methyl amines. Nevertheless, even the methylamine derivative was only 1/7 to 1/10 as active as epinephrine. On the other hand, if instead of substituting in the amino group, a hydroxy group was placed on the alpha carbon atom (XV), a greater increase in activity was noted. Compound XV possesses an asymmetrical carbon atom. The synthetic d-l form, when compared with d-l epinephrine, was found to be even slightly more active.

In the course of their investigations Barger and Dale noted that the excitatory and inhibitory effects of epinephrine derivatives did not increase and decrease in a parallel manner. Neither did they note a relationship between stability and activity. Their most basic conclusion was that sympathomimetic activity in the aromatic compounds depends upon a benzene nucleus separated from an amino nitrogen by two carbon atoms. All the sympathomimetic compounds of therapeutic value which are at present available possess this basic structure, and many represent substances which were originally investigated and prepared by Barger and Dale (compare Tables 20 and 21).

The next significant advance, which was to lead to the preparation of many new and valuable sympathomimetic drugs, was the elucidation of the structure of ephedrine. Ephedrine was found to possess many of the basic chemical features of the series of compounds studied by Barger and Dale. Thus it contains a benzene nucleus separated from an amino nitrogen by two carbon atoms. On the alpha carbon of the aliphatic chain is a hydroxy group, and on the nitrogen of the amine, a methyl group. Ephedrine, however, differs radically in that it contains one more carbon atom on the aliphatic chain. As a result, pharmacologists synthesized and investigated another series of compounds, related to those originally studied by Barger and Dale but differing in possessing three carbon atoms in the aliphatic portion of the molecule. The position of the benzene group relative to the nitrogen was retained. Outstanding sympathomimetic drugs possessing unique therapeutic applications have resulted.

The chemical relationships of all the available sympathomimetic drugs of therapeutic importance can easily be appreciated if one regards their structure in the light of the foregoing discussion. In brief, in the compounds of this series there are two important portions of the molecule, the aromatic and the aliphatic. The aromatic portion is benzene; monohydroxybenzene or dihydroxybenzene. The aliphatic portion consists of a two or three carbon atom chain. In every instance the second or beta carbon atom has an amino group attached. There may or may not be a methyl group attached to the amino nitrogen. There may or may not be a hydroxy group on the alpha carbon atom. If there is a third carbon atom, it always consists of an unsubstituted methyl group. These variables permit many variations in structure and this accounts for the large and increasing number of sympathomimetic agents. The chemical structures and interrelations of the more important of these are presented in Table 21.

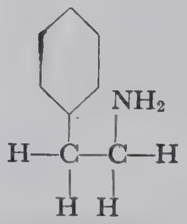
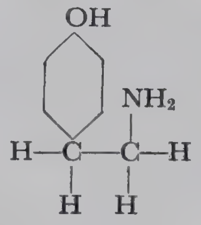
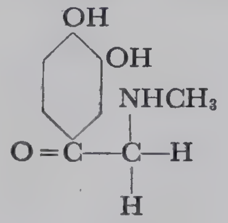
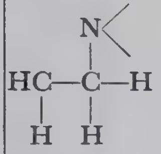
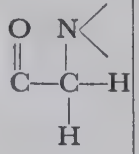
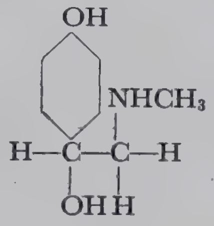
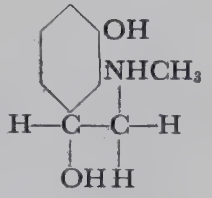
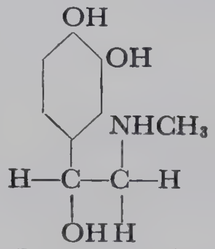
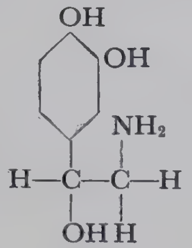
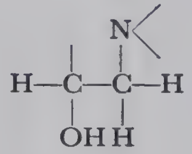
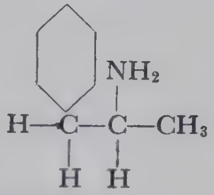
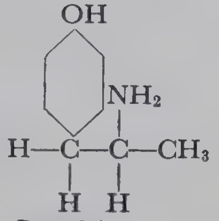
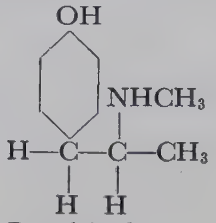
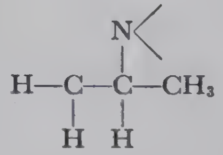
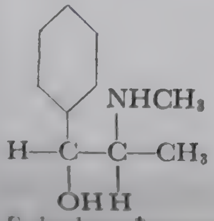
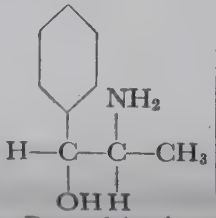
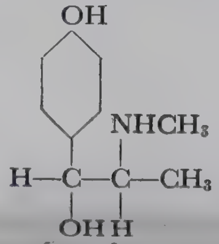
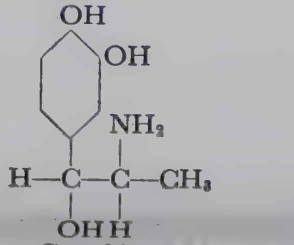
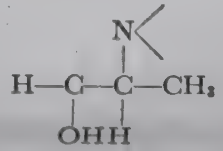
Although one can predict with remarkable accuracy from its chemical structure whether or not a compound possesses sympathomimetic activity, further relationships between structure and action are difficult to define. Various organs respond in a somewhat different manner and to a different degree to individual sympathomimetic agents. In addition, some of the compounds have marked effects on the central nervous system. Also the drugs vary in their stability. Those agents possessing a three carbon atom aliphatic chain are more resistant to destruction than those with a two carbon atom chain, and the dihydroxybenzene derivatives have the least stability. Few compounds approach epinephrine in pressor activity, but several partake of new properties which greatly increase their field of usefulness.

The derivatives of epinephrine which are employed in therapeutics represent only a small proportion of the more than 200 compounds which have been synthesized and studied. A mere attempt to point out the possible relationships between chemical structure and pharmacological action of the relatively few compounds presented in Table 21 would be beyond the scope of the present discussion. Numerous efforts have been made to correlate the various aspects of this field and such studies may eventually lead to a more basic understanding of the mechanism of action of the drugs of the epinephrine group (*see* Chen and coworkers, 1929; Hartung, 1931; Tainter, 1933, *et seq.;* Patek and Thienes, and coworkers, 1934, *et seq.;* Crimson and Tainter, 1938; Tainter and coworkers, 1939; Youmans and coworkers, 1939; Jacobsen and coworkers, 1938, 1939; Gunn, 1939; Drake, Renshaw and Thienes, 1939; and others). Of greater importance from the point of view of the application of these compounds in therapeutics is a description of the individual drugs and their pharmacological characteristics.

Mechanism of Action. Insofar as it is now understood, epinephrine acts directly on effector cells. This is clearly shown by the response of denervated organs to epinephrine (page 343), and also by the finding of Euler (1938) that the drug constricts the perfused vessels of the human placenta, which are thought to

TABLE 21

CHEMICAL STRUCTURES AND RELATIONS OF SYMPATHOMIMETIC DRUGS

AROMATIC NUCLEUS			ALIPHATIC NUCLEUS
BENZENE	MONOHYDROXY BENZENE	DIHYDROXY BENZENE	
 Phenylethylamine	 Tyramine	 Kephrine*	 
	 Synephrin  Neo-synephrin*	 Epinephrine*  Arterenol	
 Benzedrine*	 Paredrine  Paredrinol		
 			

be devoid of nerve supply. Whether epinephrine affects the receptor substance or the contractile or secretory elements of cells is not known. Certain structures in the body are stimulated by epinephrine; others are inhibited. For example, some smooth muscles are contracted, others relaxed by the drug; but whether there is a substance in the cell which determines the augmentative or inhibitory nature of the response has not been determined (page 337). Denervation of effector organs receiving adrenergic nerves greatly enhances their sensitivity to epinephrine and this fact is of considerable clinical importance in patients with postganglionic sympathetic neurectomies. The duration of action of epinephrine in the body is determined by its rate of destruction, the drug being oxidized fairly rapidly. Epinephrine and sympathin are more stable than acetylcholine in the body, and the importance of this fact in the functional organization of the autonomic nervous system has already been pointed out. A highly specific enzyme in the tissues such as that destroying acetylcholine (cholinesterase) does not exist for epinephrine. The influence of cocaine on the responses to epinephrine is discussed elsewhere as well as the effects of the *ergot* alkaloids and the relationship between *potassium* and the actions of epinephrine. Further details of the mechanism of action of epinephrine and its physiological rôle in maintaining the internal economy of the body are presented in Chapter 19.

Pharmacological Actions

In general, the actions exhibited in the body by epinephrine resemble those obtained from stimulation of adrenergic nerves. Thus, most of the responses listed in Table 17 are observed after injection of the drug in man. Sweating and pilomotor reactions, however, are not elicited, and mydriasis is not obtained except under special circumstances. Particularly prominent are the actions of the drug on the heart, blood vessels and certain smooth muscles, and these actions provide the basis for the chief therapeutic uses of the drug. So enormous is the pharmacological and physiological literature on almost every aspect of the numerous changes induced by epinephrine in bodily functions that it is only by means of a judicious restriction in the number of citations of original experiments that one can hope to present the subject within the scope of this text. For this reason also, data pertaining to the actions of the drug in man receive precedence over the more abundant results from animal experimentation.

Cardiovascular Actions. Epinephrine has numerous and complex effects upon the cardiovascular system. One of the most dramatic sights in all pharmacodynamics is the blood pressure response elicited in animals by the intravenous injection of minute amounts of the drug (Figure 39), and it is this action which so impressed Oliver and Schäfer in their original study of adrenal extracts. The heart rate is accelerated, the myocardium stimulated, the cardiac output enhanced, the cardiac rhythm often altered and the blood vessels are constricted in some areas and dilated in others. In addition, the responses are modified by the compensatory reflexes which are evoked through the carotico-aortic presso-receptor system in an attempt to return the cardiovascular status to normal. This involves increased activity of the vagal and vasodilator mechanisms. Also, inasmuch as epinephrine is thought to embody the properties of both sympathin E and sympathin I, the size of the dose administered may determine whether vasodilatation takes precedence over vasoconstriction. Finally, the presence of disease, anesthesia, and other factors modify the responses obtained. It is little wonder, then, that experimental data on the actions of the drug are sometimes conflicting.

Blood Pressure. Epinephrine is the most potent vasopressor drug known. When it is given intravenously to animals, a characteristic type of blood pressure response is evoked. Both the systolic and diastolic blood pressures rise rapidly to a peak which is proportional to the dose administered, and then quickly fall to normal. At the height of the rise, the pulse rate, accelerated at first, may be slowed markedly due to compensatory vagal discharge. This bradycardia is blocked by atropine or section of the vagi.

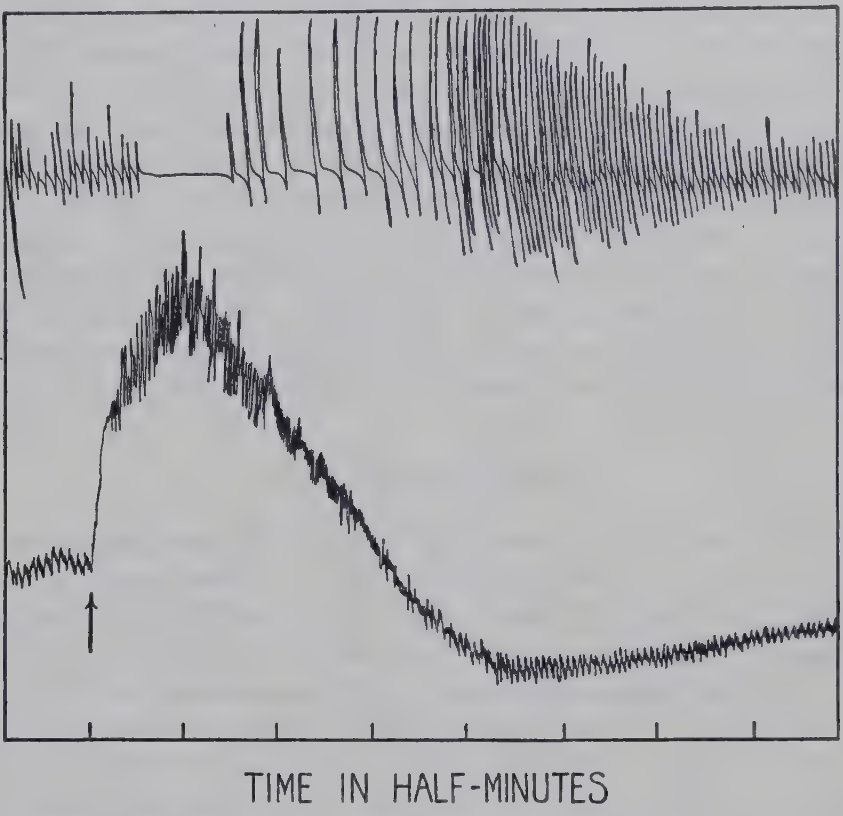


Figure 39. *The effect of intravenous epinephrine on the blood pressure and respiration.*

Dog, weight 7 kg, amytal anesthesia, vagi intact. Upper tracing, respiratory movements; lower tracing, blood pressure; time in half-minute intervals. At the arrow, 0.05 cc of a 1:1000 solution of epinephrine hydrochloride was injected intravenously. Observe the sharp rise in blood pressure, the bradycardia and increased pulse pressure at the height of the rise ("vagal effect"), the subnormal phase which appears after the pressor effect has subsided, and the evanescent character of the response to epinephrine. Note also the cessation of respiration ("epinephrine apnea") which occurs at the height of the pressor effect. (After Abel and Geiling, 1928. Courtesy of the Chemical Foundation, Inc.)

When the blood pressure has returned to normal, successive administrations of the same dose of epinephrine produce equipressor responses, in sharp contrast to the effect of repeated doses of ephedrine. The height of the rise in blood pressure is so closely proportional to the amount of epinephrine injected that the pressor response in dogs can be used for the assay of the drug. The cause of the rise in blood pressure produced by epinephrine is three-fold—direct myocardial stimulation, increased heart rate and peripheral vasoconstriction of the finer arterioles, the caliber of which controls in large measure the level of the diastolic blood pressure.

After the pressor response to epinephrine has subsided, the blood pressure does not return directly to normal, but rather there is a short period of *hypotension.* This phase of action of epinephrine is of clinical as well as academic importance. Various explanations have been offered to account for the *diphasic* action of the drug on the circulation. One is that epinephrine causes dilatation of the capillaries, an effect which is at first overshadowed by the marked arteriolar constriction. When the latter action has worn off, the more persistent capillary dilatation exhibits itself and consequently the blood pressure is reduced below normal. A more likely explanation, however, and one for which considerable collateral evidence exists, is that epinephrine combines the properties of sympathin E and sympathin I. The former constricts and the latter relaxes blood vessels. The vasodilator component of epinephrine is weaker but has a more prolonged duration of action than the vasoconstrictor component. Thus its effects are at first masked by marked arteriolar contraction, but when the excitatory action has worn off, the inhibitory factor is still present to cause vasodilatation. Under certain circumstances, the inhibitory component is predominant. Thus, when minute doses of epinephrine are injected intravenously in animals, only a fall in blood pressure may occur, especially if vascular tone is already high. In man, subcutaneously administered epinephrine uniformly causes a fall in diastolic pressure due to vasodilatation. The "after-congestion" noted in mucosae after the disappearance of vasoconstriction due to the local application of epinephrine is accounted for by the vasodilator component in the drug. Finally, the phenomenon of *epinephrine-reversal* by ergotoxine is evidence that the compound can produce vasodilatation and a fall in blood pressure when the circumstances are propitious.

When ergotoxine or ergotamine is administered to an animal in sufficient dosage before epinephrine is injected, a rise in blood pressure no longer occurs. Instead, the pressure may fall markedly, a phenomenon known as *epinephrine-reversal* (Figure 40) (page 340). This effect of certain ergot alkaloids extends to responses other than the pressor action of epinephrine and was thoroughly investigated by Dale in 1906. It is believed that ergot paralyzes the receptive mechanisms of the smooth muscles of blood vessels responding to the excitatory component of epinephrine without influencing the receptive mechanisms responding to the inhibitory or vasodilator component. This property of ergot is discussed elsewhere and the use made of it in constructing the theory of sympathin has already been mentioned. The phenomenon of epinephrine-reversal, although for years one of considerable academic interest, has no therapeutic implications. Certain other sympathomimetic agents manifest a reversal of excitatory responses after ergotoxine or ergotamine.

Cardiac Effects. Epinephrine stimulates the heart by a direct effect on the myocardium and the conduction tissue. The rate is accelerated and the rhythm often altered. Cardiac systole is more forceful, the work of the heart is increased and cardiac output is enhanced. Oxygen consumption of the heart muscle is markedly elevated. These responses, reported by many investigators employing widely different experimental technics, leave little doubt that epinephrine is a powerful cardiac stimulant.

In addition to the tachycardia caused by epinephrine, evidence of increased myocardial irritability is often noted. The drug speeds auriculoventricular conduction, decreases the grade of A-V block occurring as a result of disease, drugs or vagal stimulation, and excites the idioventricular pacemaker in patients with complete heart block. Premature systoles of ventricular origin occur and may herald more serious types of ventricular rhythms. When other factors affecting cardiac irritability are present, such as anesthesia or disease, epinephrine is particularly likely to precipitate ventricular rhythms such as extrasystoles, tachycardia and even ventricular fibrillation. The dangers and precautions incident to the endogenous release of epinephrine or the use of the drug during anesthesia with certain agents are presented in detail elsewhere (pages 61, 93) (*see* Meek, 1940).

The effect of epinephrine on the *electrocardiogram* in animals has received considerable attention. For example, in unanesthetized cats receiving the drug intramuscularly, marked displacement of the S-T segment above or below the isoelectric level occurs. These changes can be abolished by nitroglycerin. Milles and Smith (1937) injected epinephrine into the saphenous vein or directly into the coronary artery in dogs. The minimal effect noted was a decrease in amplitude of the T wave. More marked cardiac action of the drug was manifested in a diphasic form of and directional changes in the T waves, deviation of the S-T segment from the isoelectric line, ventricular extrasystoles, and occasionally ventricular fibrillation. Inasmuch as direct measurements showed that the coronary flow was increased during the period when epinephrine was altering the electrocardiogram, the authors concluded that the electrical changes, which simulate those encountered in patients with angina pectoris, must be due to a relative myocardial anoxia caused by the increased demands for oxygen of the epinephrine-stimulated myocardium. This conclusion is in keeping with the known accelerated consumption of oxygen by heart muscle and the increased amount of cardiac work after epinephrine.

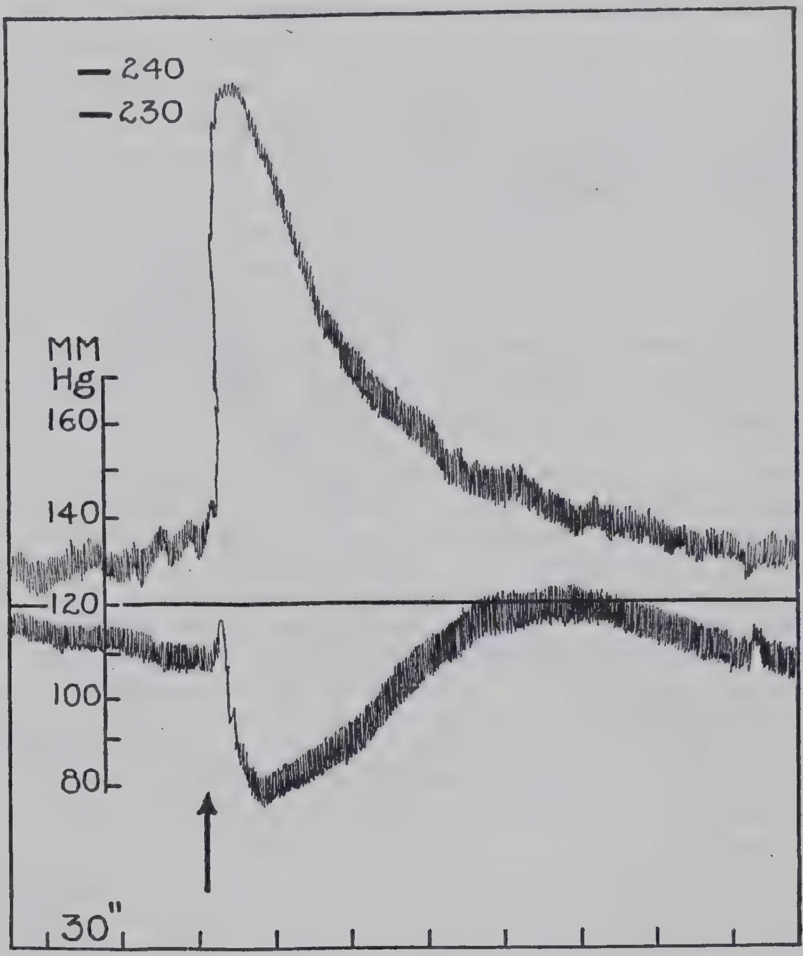


FIGURE 40. *The reversal by ergotoxine of the pressor response to intravenous epinephrine in a pithed cat.*

The upper tracing shows the effect of an injection of 0.025 mgm of epinephrine on the carotid blood pressure. The lower tracing depicts the fall in blood pressure which occurs after the injection of epinephrine (0.1 mgm) when 10 mgm of ergotoxine are previously administered. (After Dale, 1913. Courtesy of the *Journal of Physiology*.)

Vascular Effects. The chief vascular action of epinephrine is exerted on the smaller arterioles, although capillaries, veins and larger arteries also respond to the drug. Various vascular beds react differently. The vessels of the *skin* and *mucosa* are constricted and this is obvious after local injection or application as well as after systemic administration of the drug. Cutaneous vasoconstriction caused by epinephrine endogenously released from the adrenal medulla accounts for the expressions "pale with fright" and "white with anger." The blood vessels of *skeletal muscles* are dilated by epinephrine, a matter of importance in the economy of the body when flight or fight is necessary. The *splanchnic bed* is constricted by the drug. The *cerebral* and *retinal* vessels are also constricted by epinephrine and the *pulmonary vessels,* although less responsive to vascular agents than other vessels, tend to contract. The *glomerular arterioles* of the kidney constrict after epinephrine but the resulting effect on urine formation depends on the relative intensity of the effects on the afferent and efferent arteriolar limbs. If the predominant action of the drug is on the afferent arteriole, antidiuresis is likely to occur whereas constriction of the efferent arteriole increases filtration pressure and produces diuresis.

The response of the *coronary arteries* to epinephrine depends upon the species being examined and the technic employed. Both constriction and dilatation have been reported to occur after the drug, but dilatation is the predominant response. Melville (1933) reported that both epinephrine and ephedrine caused vasodilatation of the coronaries and abolished the coronary vasoconstriction induced by posterior pituitary extract. Anrep and coworkers (1936), using a direct flow method, observed coronary vasodilatation after epinephrine and Gollwitzer and associates (1936) found that both sympathetic nerve stimulation and epinephrine resulted in increased coronary blood flow. Katz and coworkers (1938) noted that the coronary flow in isolated perfused cat hearts decreased in some preparations in response to epinephrine but increased in others. In 23 dog hearts, however, the drug caused only coronary vasodilatation, occasionally preceded by a transient vasoconstriction. Boyer and associates (1939) injected epinephrine directly into the coronary arteries in 16 dogs and in each case the result was an enhanced coronary flow during diastole which preceded and persisted after the elevation of blood pressure. The rate of flow during systole in most instances was decreased. Given intravenously, epinephrine produced an increase of from 10 to 20 per cent in coronary blood flow. Essex and collaborators (1940), using trained dogs with thermostromuhr units implanted on the coronary arteries, observed that epinephrine markedly increased coronary blood flow (occasionally over 200 per cent), the augmented flow being accompanied by an accelerated heart rate.

The response to epinephrine, however, cannot be employed as an index of the effects of sympathetic nerve impulses on the caliber of the coronary arteries. It is usually stated that the sympathetic nerve impulses cause coronary vasodilatation whereas vagal impulses cause vasoconstriction (Anrep and Segall, 1926; Kountz and associates, 1934; and others). This concept has recently been questioned by Katz and Jochim (1939) who found in the dog heart, an organ similar at least experimentally to the human heart, that vagal stimulation produced only vasodilatation but that stimulation of the sympathetic fibers elicited either vasoconstriction or vasodilatation. The only coronary vasoconstrictor fibers were thus adrenergic in character and ran in the sympathetic pathways (Katz and Lindner, 1939). This concept is important for the surgical treatment of angina pectoris, and it is interesting to note in passing that Raney (1939) has devised an operation for angina pectoris which brings relief from pain after preganglionic section of the efferent sympathetic outflow to the heart, the afferent sympathetic fibers being left largely intact. The procedure involves the section of the rami communicantes of the second to and including the fifth thoracic sympathetic ganglion and the cutting of the sympathetic chain between the fifth and sixth ganglia.

Cardiovascular Responses in Man. The cardiovascular responses in man observed after the administration of epinephrine have been studied by numerous workers. The results obtained by Blumgart (1932) and Starr and associates (1937) may be taken as representative. Blumgart injected 0.5 to 1.0 cc of a 1:1000 solution subcutaneously into 10 normal subjects under strictly basal conditions. The pulse rate increased from 12 to 24 beats per minute (average of 16) in eight of the 10 subjects, only two failing to develop a tachycardia. The systolic blood pressure rose in all instances from 10 to 70 mm of mercury, the average being 38. The diastolic pressure remained unchanged in three subjects but *fell* from five to 35 mm of mercury in the remaining, an average of 14. Thus the pulse pressures in the group as a whole increased markedly from an average of 46 mm of mercury to 94. The speed of blood flow was accelerated in every subject, the increase varying from 30 per cent to 143 per cent and averaging 76. The peripheral blood flow, as gauged by the arm to heart circulation time, was enhanced in eight of the 10 individuals, an average of 105 per cent. In two, the circulation time was slightly decreased.

Starr and coworkers obtained essentially similar results in a careful study of six patients, several of whom had cardiovascular disease. Epinephrine was injected subcutaneously in an average dose of 0.7 cc of a 1:1000 solution. The results in comparison with the responses to ephedrine are shown in Table 22. The pulse rate, cardiac output, stroke volume, and left ventricular work per minute and per beat were all increased significantly. The systolic pressure rose somewhat but particularly noteworthy is the *fall* in diastolic pressure and the decreased peripheral vascular resistance. These facts indicate that epinephrine is a powerful cardiac stimulant in man and that after subcutaneous injection the diastolic pressure usually falls due to the vasodilatation in certain vessels predominating over the vasoconstriction which undoubtedly occurs in other areas. Apparently, when absorbed slowly from hypodermic sites of injection, the ability of epinephrine to produce vasodilatation takes precedence over constriction.

Table 22

CARDIOVASCULAR, RESPIRATORY AND METABOLIC EFFECTS OF EPINEPHRINE AND EPHEDRINE IN HUMAN SUBJECTS UNDER BASAL CONDITIONS

	Epinephrine Hydrochloride * (0.7 Cc [1:1000] Subcutaneously)		Ephedrine Sulphate ** (53 Mgm Subcutaneously)	
Function	Decrease %	Increase %	Decrease %	Increase %
Pulse rate		21.0		9.7
Systolic pressure		4.8		14.8
Diastolic pressure	14.5			5.2
Cardiac output		51.7		27.0
Stroke volume		22.7		15.7
Left ventricular work per minute		52.4		41.2
Left ventricular work per beat		26.2		32.7
Heart volume	4.0		1.0	
Metabolic rate		30.4		14.2
Arteriovenous oxygen difference	13.3		8.6	
Respiratory rate		26.0		9.2
Respiratory volume		42.0		19.4
Peripheral circulatory resistance	35.1		12.9	

* Average results in six patients.
** Average results in six patients.
Starr, Gamble, Margolies, Donal, Joseph and Eagle, 1937.

When epinephrine is injected *intravenously* in man, both the systolic and diastolic pressures rise markedly, optical manometric methods showing that the blood pressure sometimes reaches levels of 400/300 mm of mercury for a brief period. Due to inertia, these high tensions cannot be recorded accurately with mercury manometers. Great care must therefore be exercised to avoid the error of injecting epinephrine into a vein when subcutaneous injection is desired Cerebrovascular hemorrhages have occurred from this accident.

The ability of epinephrine to cause changes in the *electrocardiogram* and to induce attacks of *pain of cardiac origin* has been studied by several investigators both in normal persons and in those with angina pectoris. Clough (1919) observed that epinephrine decreased the T wave in all leads in the majority of normal persons and in patients with "irritable" hearts. Several clinical reports have indicated that patients with angina pectoris are likely to develop typical anginal attacks after injection of epinephrine. Thus, Levine and coworkers (1930) noted that one cc of a 1:1000 solution of the drug given subcutaneously resulted in typical pain in all but one of 11 patients with angina pectoris, and that the T wave increased slightly in amplitude. In 10 control patients of the same age group but without angina pectoris and in a second control group of 10 normal young adults, anginal pain did not occur and the T wave in Lead II showed a tendency to decrease. These investigators suggested that the drug might prove serviceable as a diagnostic test for angina pectoris in patients in whom the diagnosis is uncertain. Katz and collaborators (1932), however, point out that the electrocardiographic changes noted are not characteristic of those occurring during spontaneous angina pectoris, a depression of the S-T segment being the usual finding and changes in the T wave being variable. Katz and associates noted precordial distress in two of six normal persons after injections of epinephrine and that three of six patients with angina failed to develop pain after the drug. The most characteristic change produced by epinephrine in the electrocardiogram in the patients with angina was a deviation downward of the S-T segment similar to that noted during spontaneous attacks of angina. This finding, however, was not constant and occurred in an individual without angina. The T wave was decreased in amplitude in practically all cases, normal as well as those with angina pectoris. It was concluded that the production of pain by epinephrine is not a reliable index of angina pectoris and that the electrocardiographic changes are not pathognomonic for the syndrome. The test also cannot be advised because of the severe reactions which may occur.

Respiratory Effects. Epinephrine lacks the property of stimulating the respiratory center which characterizes certain other sympathomimetic amines, and consequently has no appreciable direct effect on the respiratory rate. When the drug is given intravenously to animals, a period of apnea may follow ("epinephrine apnea") due to the reflex inhibition of respiration caused by the increased pressure in the carotid sinus and cardio-aortic area (Heymans and Bouckaert, 1930). The drug can influence respiration in other ways, however, particularly through relaxation of the bronchial musculature. This antispasmodic action is clearly evident when the bronchial muscles are in a state of heightened contraction or spasm due to vagal stimulation, drugs such as pilocarpine, choline esters, etc., or disease such as bronchial asthma. Despite the theoretical reasons why atropine should be ideal in counteracting bronchial spasm resulting from vagal stimulation, epinephrine is markedly superior in causing immediate and effective relaxation. It is evident from Figure 41 that epinephrine is not only effective in counteracting vagal-induced bronchial constriction but that during the period of its action further cholinergic stimulation may be entirely without effect. No more potent bronchodilating agent than epinephrine is available to the physician. In addition, epinephrine may increase vital capacity by lessening the edema of congested bronchial mucosa.

Respiratory volume may be markedly increased by the injection of epinephrine even when patients are not suffering primarily from disturbances in respiratory exchange. Thus, Starr and associates noted in the experiments cited that respiratory minute volume was enhanced an average of 42 per cent in their six subjects, and that the rate of respiration increased 26 per cent (Table 22). In a study of the total pulmonary capacity and its subdivisions in five patients during acute attacks of bronchial asthma before and immediately after the subcutaneous injection of 0.75 cc of 1:1000 solution of epinephrine, Hurtado and Kaltreider (1934) observed that the decrease in the absolute and relative value of the vital capacity and the marked increase in the mid capacity and residual air which characterize the acute respiratory distress of bronchial asthma are rapidly alleviated by the drug. Thus, the vital capacity increases, the mid capacity and residual air are decreased and symptoms are thereby alleviated. These effects of epinephrine are graphically depicted in Figure 42. Essentially similar results have been reported by Means (1924) and Anthony (1930). Improved pulmonary function as indicated by increased vital capacity and maximum breathing capacity has also been reported to occur following the inhalation of vaporized epinephrine solution by patients with asthma and emphysema (Richards and coworkers, 1940).

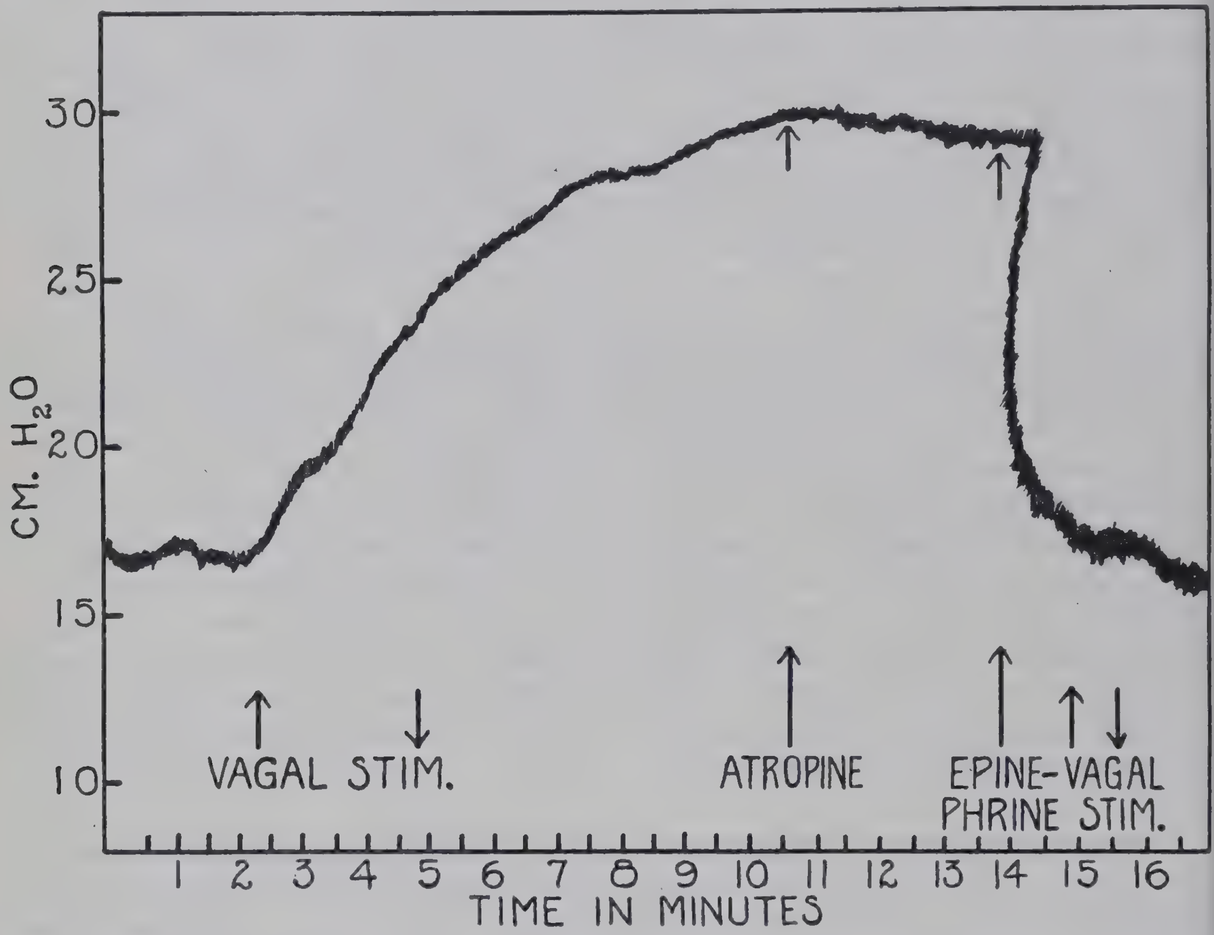


FIGURE 41. *The comparative value of atropine and epinephrine as bronchial antispasmodics.*

Perfused guinea pig lung. Bronchial spasm produced by stimulation of the vagus, and recorded by measuring the bronchial resistance in centimeters of water. Moderate amounts of atropine fail to relax the bronchial muscle, whereas epinephrine is immediately effective. During the period of action of epinephrine, further vagal stimulation is incapable of causing bronchial contraction. (After Thornton, 1932. Courtesy of the *Quarterly Journal of Experimental Physiology* and Sir Edward Sharpey Schafer's Trustees.)

Metabolic Effects. Epinephrine is a metabolic stimulant, increasing oxygen consumption. It promotes the combustion of carbohydrate and therefore the respiratory quotient rises. Body temperature is also increased. The basal *metabolic rate* in man is elevated by the subcutaneous injection of average doses, Blumgart (1932) noting an increase of 16 per cent in six normal subjects and Starr and coworkers (1937) observing an increase of 30.4 per cent (Table 22). The calorigenic action is unrelated to stimulation of the thyroid. It may be due to a direct action of epinephrine on cellular oxidations, but it is said not to occur in hepatectomized animals.

The ability of epinephrine to elevate the *blood sugar* and to cause *hyperglycemia* and *glycosuria* is well known. These phenomena occur as a result of mobilization of sugar from the liver. The drug can thus relieve insulin hypoglycemia, provided the liver stores of glycogen are adequate. Epinephrine also reduces the muscle stores of glycogen. For this reason, when injected into a long-fasting animal, the drug may increase liver glycogen at the expense of the muscle glycogen. The influence of epinephrine on carbohydrate metabolism in mammals has been intensively studied by many investigators, especially by Cori and Cori (*see* review by Cori, 1931).

Action on Smooth Muscles. The effects of epinephrine on the smooth muscles of blood vessels and bronchi have already been described. The musculature of the *gastro-intestinal tract* is relaxed by epinephrine and that of the pyloric and ileocecal sphincters, as a rule, is contracted. Intestinal tone is diminished and the frequency and amplitude of peristaltic waves are decreased. The sphincters, however, may react in a variable manner to epinephrine, as they do to other autonomic drugs and to autonomic nerve impulses, depending on their level of functional activity at the time (page 466). The effects of epinephrine on the alimentary canal have no therapeutic applications because they are elicited only by doses which cause marked cardiovascular responses.

The musculature of the *splenic capsule* is contracted by epinephrine. This reduction in size of the spleen accounts for the increase in the number of red blood cells and the increase in blood viscosity observed in the peripheral circulation after administration of the drug. Contraction of the vascular spaces of the *bone marrow* may also contribute to the epinephrine-induced erythremia. The secretion of epinephrine provides a physiological mechanism for increasing the amount of circulating hemoglobin during acute anoxia, hemorrhage, etc.

The *detrusor muscle* of the urinary bladder is relaxed by epinephrine, the *trigone* and *sphincter* being contracted. The *uterine musculature* exhibits variable responses to epinephrine, dependent on the species examined, the time of the menstrual cycle or the state of gestation. Both the gravid and non-gravid uterus in many animals are stimulated, but in certain species the non-gravid uterus is relaxed. Uterine relaxation, for example, can be observed regularly in the non-pregnant cat (Figure 29), and the constancy of this response provides a means of identifying sympathin I. The human uterus is generally contracted by epinephrine, whether pregnant or non-pregnant, but this action is not marked and rarely, if ever, interferes with the use of the drug for other purposes, if needed, in pregnant patients. When tested *in vitro,* muscle strips from human uteri usually contract in response to epinephrine regardless of the day of the menstrual cycle at the time of hysterectomy (Miller and coworkers, 1937).

Miscellaneous Actions. Epinephrine has very little stimulating effect on the *central nervous system* and thus is not useful as an analeptic or as a central respiratory and vasomotor stimulant. Nevertheless, restlessness, apprehension, headache and tremor may occur in some individuals after therapeutic doses. The *secretory effects* of epinephrine on glands are negligible, secretion usually being inhibited as a result of the accompanying vasoconstriction (Table 17). Sweating and pilomotor responses are not seen in man after administration of epinephrine but may be quite marked in certain species of animals. Thus marked sweating occurs in the horse and sheep. *Mydriasis* is noted in human beings to whom epinephrine is given only when the radial fibers of the iris are denervated as a result of interruption of the superior cervical sympathetic nerve fibers or when the iris is sensitized by thyroxin, as in hyperthyroid individuals.

Absorption, Fate and Excretion. *Absorption.* Epinephrine is not absorbed from the enteric mucosa due to its destruction by the gastro-intestinal juices. Absorption occurs from the subcutaneous tissues and can be hastened by massage of the injection site. Absorption is appreciably delayed by suspending the drug in an oil. Epinephrine administered intramuscularly is more rapidly absorbed than from subcutaneous tissue. Although systemic effects are not observed after local application of the drug to mucosal surfaces, marked local vasoconstriction is observed. When strong solutions (one per cent) are nebulized and inhaled, the actions of the drug are restricted to the respiratory tract, and although systemic reactions may occur, these are usually mild unless large amounts or stronger solutions are employed.

Fate. The exact fate of epinephrine in the body is unknown. The drug is rapidly destroyed in the body within a few minutes and ligation of the renal vessels, hepatectomy, etc., do not affect the rate of inactivation. It appears that epinephrine is inactivated in the tissues by oxidation. The enzyme thought to be responsible for the oxidation has been termed "amine oxidase" (Blaschko and coworkers, 1937; Blaschko, 1938; Richter, 1937). This oxidase apparently catalyzes the destructive deamination of a large number of different types of amines including certain sympathomimetic amines related to epinephrine (tyramine, phenylethylamine, synephrin), but not others (ephedrine, benzedrine). It is distinct from both amino acid oxidase and histaminase. The enzymatic oxidation of epinephrine (by peroxidase) results in the simultaneous loss of excitatory and inhibitory properties of the molecule (Blaschko and Schlossman, 1940).

Amine oxidase is definitely not specific for epinephrine and probably represents the system mainly responsible for the detoxication of amines in the body. The results of Richter and Tingey (1939) cast some doubt on the rôle played by amine oxidase in the oxidative destruction of epinephrine and sympathin in the tissues. Evidence from *in vitro* experiments appears to indicate that the rate of oxidation by this enzymatic system is not sufficiently rapid to account for the speed of disappearance of epinephrine *in vivo.* Amine oxidase exists especially in the liver and intestine (in ruminants), suggesting that it is concerned primarily with the detoxication of amines formed by bacterial action in the gut. Until information is obtained concerning the distribution of amine oxidase at adrenergic nerve endings similar to the data existing for the concentration of cholinesterase at cholinergic nerve endings, any conclusion concerning the physiological rôle of amine oxidase in the destruction of epinephrine and sympathin *in vivo* must be held in abeyance.

Excretion. Little is known of the excretion of epinephrine or its breakdown products. *Protocatechuic acid* has been isolated from the urine of rabbits injected with epinephrine and this may represent the inactive oxidation product (Weinstein and Manning, 1937).

Preparations. A variety of preparations of epinephrine is available to the physician and the terminology employed is often confusing. *Epinephrine* is the official U.S.P. term, *Adrenaline,* the B.P. term. Unfortunately, certain trademarked names (*e.g.,* "adrenalin," "suprarenin") are used synonymously with epinephrine in common medical parlance.

Epinephrine, U.S.P., B.P. (*Adrenaline*), is the levorotatory form of methylaminoethanolcatechol. It is a white or light brown, microcrystalline, odorless powder which gradually darkens on exposure to air. The drug is slightly soluble in water and in alcohol and is insoluble in the usual organic solvents as well as in fixed or volatile oils. The U.S.P. and B.P. do not specify the source of the drug, which may be obtained from the suprarenal medulla of domestic animals or prepared synthetically. Epinephrine forms water-soluble salts with acids. The drug is unstable in alkaline solution due to oxidation. Oxidizing agents turn epinephrine a red, pink or violet color which changes to brown. The drug should be preserved in air-tight containers and protected from light. Only levorotatory epinephrine is employed clinically. The d-l (racemic) synthetic form is only one-half and the dextrotatory compound is only one-eighteenth as potent as the official drug.

Epinephrine is usually administered in the form of its soluble salts. Epinephrine base, however, has been incorporated as a suspension of powdered epinephrine in peanut oil (*Epinephrine in Oil*) in a concentration of 2.0 mgm per cc (0.2 per cent solution) for intramuscular (preferable) or subcutaneous injection when prolonged systemic effects are desired. The preparation is not official but is described in N.N.R. Epinephrine in oil is sometimes referred to as "slow epinephrine."

Solution of Epinephrine Hydrochloride, U.S.P., B.P. (*Solution of Adrenaline Hydrochloride*), is a 1:1000 sterile solution in distilled water for parenteral administration. The solution is a nearly colorless, slightly acid liquid which withstands a short period of boiling and keeps fairly well when undiluted and aseptic. It gradually turns dark on exposure to air and light and deteriorates in a few hours when diluted. The solution must be rejected if the color has changed or a precipitate has formed. An acceptable preservative is added (usually 0.5 per cent chlorbutanol or sodium bisulfite) and the solution is usually dispensed in sterile ampules containing one cc (1.0 mgm). Five, 10 and 30 cc vials are also marketed. The U.S.P. requires assay of the solution by means of the blood pressure response in the dog.

Epinephrine hydrochloride is only official in the form of the 0.1 per cent aqueous solution described. However, other preparations are available for use. The N.N.R. includes *hypodermic* tablets of the drug, each containing 0.33 or 1.0 mgm, so that addition of 0.33 or 1.0 cc of water, respectively, will yield a 1:1000 solution. Epinephrine bitartrate and epinephrine borate are also marketed in tablet form and in solution. Epinephrine hydrochloride is also available in a more concentrated solution than the official one. Thus a 1.0 per cent solution in 0.9 per cent sodium chloride is available for inhalation therapy of asthma—*Solution of Epinephrine Hydrochloride 1:100* (*N.N.R.*)—supplied in five cc ampules. This preparation must not be confused with the one used for parenteral injection and is 10 times as strong. Finally, epinephrine hydrochloride is marketed in the form of an *inhalant* (1:1000 in glycerin), *ointment* (1:1000 in petrolatum) and *suppository* (1:1000 in cacao butter).

Routes of Administration and Dosage. Epinephrine is inactive when taken *orally* and is used by this channel only when the local effects on the gastric mucosa are desired. The *subcutaneous* route is the one most frequently employed. A 1:1000 (0.1 per cent) solution is used. The usual adult dose ranges from 0.2 to 0.5 cc (0.2 to 0.5 mgm). Epinephrine in oil (0.2 per cent solution) may also be adminstered subcutaneously, although the intramuscular route is preferable when continued administration is necessary. The dose for adults is 0.75 cc to 1.5 cc (1.5 to 3.0 mgm). The advantages of epinephrine in oil are discussed under the use of the preparation in the treatment of asthma. The *intravenous route* is rarely employed. If the drug is given by vein, it must be greatly diluted and given *very* *slowly*. The dose varies with the results desired, but usually is not greater than 0.25 mgm. *Intracardiac* injection is occasionally employed in extreme emergencies for purposes of resuscitation. Administration of epinephrine by *inhalation* is advantageous under certain circumstances. A 1.0 per cent solution is employed. Epinephrine may be applied *locally* to mucous membranes or abraded surfaces in the form of an aqueous solution, inhalant, suppository or ointment, a 1:1000 concentration generally being employed.

Toxicity, Precautions and Contraindications. Certain mild untoward reactions may occur from the administration of epinephrine. These consist of fear, anxiety, tenseness, restlessness, throbbing headache, tremor, weakness, dizziness, respiratory difficulty, and palpitation. The effects subside rapidly with rest, quiet and reassurance, but nevertheless the patient is often alarmed and probably should be forewarned. Hyperthyroid individuals are particularly susceptible to the untoward responses noted after epinephrine.

More serious accidents consist of cerebral hemorrhage and cardiac arrhythmias. The use of large doses or the accidental intravenous injection of epinephrine may result in cerebral hemorrhage due to the sharp rise in blood pressure. Flexner and Schneider (1938) record subarachnoid hemorrhage in a young woman following the subcutaneous injection of 0.5 cc of a 1:1000 solution of the drug and Keeney (1939) has observed a complete right-sided hemiplegia and loss of vision in the right field in a young man after a similar dose injected during an asthmatic attack. Obviously, care should be exercised in using the drug in patients with advanced cerebral arteriosclerosis.

Ventricular arrhythmias may follow the administration of epinephrine and if ventricular fibrillation develops it is usually fatal. This arrhythmia is particularly prone to occur if the drug is used unwisely during surgical anesthesia or in individuals with organic heart disease. Patients with long-standing bronchial asthma and a significant degree of emphysema who have reached the age in which degenerative heart disease is prevalent must be given epinephrine only with considerable caution (Smith and Paul, 1938). In patients suffering from medical or surgical shock, the drug may accentuate the underlying disorder (pages 588). Those with hypertensive heart disease or hyperthyroidism are prone to be hypersusceptible to the pressor effect of epinephrine. Anginal pain due to epinephrine frequently occurs in patients with angina pectoris (Levine and coworkers, 1930; Cottrell and Wood, 1931; Katz and associates, 1931). This is probably due to the great increase in cardiac work resulting from the actions of the drug. In psychoneurotic individuals, existing symptoms are often markedly aggravated by epinephrine (Kraines and Sherman, 1940).

Therapeutic Uses

Epinephrine has a wide variety of clinical uses. In general, these are concerned with the actions of the drug on the blood vessels, heart and bronchial muscles.

Clinical Use of Vascular Effects. *Control of Hemorrhage.* The vasoconstrictor action of epinephrine is useful in the control of superficial hemorrhages of the skin and mucous membranes. The drug may be employed in freshly prepared solutions ranging in concentration from 1:50,000 to 1:2000 and applied directly to accessible bleeding surfaces in the form of a spray or on cotton or gauze pledgets. It is useful in operations on the nose, throat and larynx where considerable clearing of the operative field is obtained by diminution of hemorrhage and shrinkage of mucous membranes. The local hemostatic action of epinephrine is effective only against bleeding from smaller arterioles and capillaries, and hemorrhage from larger vessels or venous oozing is not readily controlled. Obviously there is no rationale for the systemic administration of epinephrine in internal hemorrhages. The drug has been given orally in gastric hemorrhage, the action, if any, being confined locally to the mucosa. Unless the bleeding is from very small mucosal vessels the benefit to be derived from this practice is highly questionable. Epinephrine solution, however, has been given orally for the relief of protracted vomiting due to gastritis, as in the bilious type of pernicious malaria. Benefit is probably due to shrinkage of the hyperemic and congested gastric mucosa as a result of local vasoconstriction.

Congestion of the Nasal Mucosa. Epinephrine causes marked vasoconstriction and blanching when its solutions are applied to the nasal mucosa. It is thus useful in the treatment of the mucosal congestion accompanying hay fever, allergic rhinitis, acute coryza, sinusitis, etc. Oily solutions of epinephrine are more persistent in action. A phase of after-congestion often occurs when the vasoconstrictor effect has disappeared. The significance of this has been explained. The short duration of action of epinephrine and the tendency to cause after-congestion limit its value for shrinkage of the nasal mucosa. Other sympathomimetic agents have been found more serviceable for this purpose. Epinephrine has the advantage, however, of being non-irritating. Thus its solutions are useful in overcoming marked vascular congestion of the conjunctiva.

Use with Local Anesthetics. Epinephrine is widely employed in solutions of local anesthetics. By causing vasoconstriction, the drug limits the absorption of the local anesthetic and thus prolongs the duration of anesthesia, decreases the amount of anesthetic needed and lessens the danger of systemic toxicity. Furthermore, hemorrhage from the ensuing surgical procedure is decreased. The resulting bloodlessness of the operative field, however, may make adequate surgical hemostasis more difficult because small vessels, constricted by epinephrine, may escape detection. These are potential bleeders when the vasoconstrictor effect of epinephrine has worn off and after-dilatation occurs. Epinephrine is particularly indicated when procaine and other synthetic congeners are injected because, unlike cocaine, these anesthetics lack a vasoconstrictor action. Concentrations of epinephrine of from 1:100,000 to 1:20,000 are incorporated in the anesthetic solution. Further details of the combined use of epinephrine and local anesthetics are discussed in connection with the latter drugs.

Shock. The mechanism of the shock syndrome is described in detail on page 586 and it is there pointed out that the primary disturbance is a sharp discrepancy between the amount of circulating blood volume and the volume capacity of the circulatory system. Epinephrine has little place in the therapy of shock because the arterioles are already constricted maximally in a reflex attempt to maintain the blood pressure. Indeed, the drug may accentuate the basic pathological physiology of the syndrome by further increasing the degree of tissue anoxia through constriction of arterioles (*see* also epinephrine in nitrite syncope). Much safer and more effective measures are available for the management of shock than the use of vasopressor drugs.

Clinical Use of Cardiac Effects. *Heart Block with Syncopal Seizures.* In *Stokes-Adams disease,* epinephrine may relieve the syncopal seizures and give symptomatic relief by virtue of its cardio-accelerating property. Before using epinephrine in patients with complete auriculoventricular dissociation, however, one must make certain that the syncopal attacks are due to periods of asystole or marked bradycardia rather than to short runs of abnormal ventricular rhythms of a prefibrillation type, in which event epinephrine may precipitate fatal ventricular fibrillation. Caution is also required in patients with hypertension, marked arteriosclerosis or other organic cardiovascular lesions.

The usual dose is 0.3 to 0.6 cc of a 1:1000 solution injected subcutaneously and repeated at intervals as needed. Somewhat larger amounts of epinephrine in oil may also be employed for more prolonged effects. Larger doses than those providing relief do not result in greater acceleration of the idiopathic ventricular rate. Intravenous injection of epinephrine is not to be used, except perhaps when death appears imminent due to prolonged asystole. Under such circumstances, the drug may be life-saving. The good effects of therapy may persist for many hours and the cardiac rate may be maintained above 30 beats per minute, sometimes as high as 50 or 60, for days at a time with epinephrine therapy. Epinephrine speeds the ventricular rate either by diminishing the grade of auriculoventricular block, or, more commonly, by stimulating the idioventricular pacemaker. The block is not abolished as a rule, although normal sinus rhythm may be restored in rare instances.

Both the auricular and ventricular rates are increased by epinephrine in complete heart block. Whereas the effect of the drug on the rate of auricular contraction bears no relation to the initial auricular rate, there is a direct correspondence between the drug-induced acceleration of the ventricle and the initial idioventricular rate. The slower the original ventricular rate, the more pronounced is the accelerating effect of epinephrine. When the initial rate is high, epinephrine has little further action on it. This is the exact reverse of the situation obtained in the use of atropine in complete heart block (page 476) and again illustrates that the responses of the heart to drugs are often conditioned by the level of functional activity existing at the time.

Resuscitation in Cardiac Arrest. Epinephrine is too often looked upon as an effective agent in reviving patients apparently dead from drowning, electric shock, anesthetic accidents, etc. While it is true that the drug occasionally produces dramatic results, much more often it fails entirely. This is due either to the fact that the arrested heart is beyond resuscitation or to the precipitation of ventricular fibrillation by the large doses of epinephrine administered intravenously or intracardially. If heart sounds are still audible, small doses of epinephrine (0.05 to 0.2 cc of a 1:1000 solution) may be diluted and injected very slowly intravenously. If heart sounds are unobtainable, intracardiac injection of 0.5 cc may be performed. When death is imminent, heroic measures are justified despite the potential risk of ventricular fibrillation. If asystole occurs during the early phase of inhalation anesthesia, it is quite likely that ventricular fibrillation already exists and little benefit can then be expected from injecting epinephrine. Cardiac massage, if possible, artificial respiration and other emergency measures should also be employed.

Acute Cardiac Failure. Epinephrine has occasionally been employed as an emergency stimulant in the treatment of acute cardiac failure. More often than not, however, circulatory failure is peripheral in nature and comes under the category of shock, rather than being due to primary weakness of the myocardium. Under these circumstances, the measures employed in shock therapy are to be instituted. Nevertheless, the mechanism of acute cardiac failure is often complicated, as in the type occurring during the course of an acute infectious disease, and there may be present a distinct factor of acute myocardial decompensation as well as vasomotor paralysis or capillary dilatation due to toxic agents. After the usual measures employed in circulatory collapse have been instituted and if epinephrine is still decided upon as a myocardial stimulant, it should be administered subcutaneously (0.25 to 0.5 cc of a 1:1000 solution). Occasionally, the drug has been added in very small amounts to the intravenous solutions used to restore blood volume. It requires considerable discretion to determine whether epinephrine is required in emergencies of this sort, and one must weigh carefully the rôle played in the acute circulatory failure by the myocardial decompensation as opposed to the peripheral circulatory factors, remembering that "more get well than are cured."

Cardiac Asthma. In cardiac asthma (dyspnea due to left ventricular weakness) therapy is designed to restore myocardial compensation and relieve the strain on the left ventricle. In the acute form of the disorder, such as severe attacks of paroxysmal nocturnal dyspnea, in addition to the use of morphine, theophylline, nitroglycerin, cardiac glycosides, intravenous hypertonic glucose, phlebotomy and other physical measures, etc., epinephrine may occasionally be used with caution as an adjunct. This is particularly true in cases where there appears to be an added element of bronchial spasm contributing to the dyspnea and asthmatic breathing. From 0.2 to 0.3 cc of a 1:1000 solution may be injected subcutaneously. The drug is definitely contraindicated in patients with coronary thrombosis and angina pectoris. Although hypertensive cardiovascular disease is usually the syndrome underlying cardiac asthma, the judicious use of epinephrine does not seem further to elevate the blood pressure and a paradoxical fall with relief of the asthma may even occur. It should definitely be appreciated, however, that epinephrine is of minor value in comparison with the more usual and effective measures listed above. Benefit from the drug can be expected only when it is used wisely in those cases where bronchial spasm is superimposed on the basic pulmonary vascular congestion due to the left ventricular failure. The use of epinephrine carries with it clear contraindications in patients with heart disease, and the drug may be harmful in cases of frank pulmonary edema.

Allergic Disorders. *Bronchial Asthma.* Epinephrine occupies an unrivaled place among drugs used in the symptomatic therapy of bronchial asthma. It is a more potent bronchial antispasmodic than any of its congeners and the mechanism by which it affords relief has already been outlined. Likewise the changes in pulmonary ventilation occurring after injection of the drug during the acute asthmatic attack have been described (Figure 42). Regardless of the manner in which epinephrine is administered, the smallest effective dose should be employed because patients with bronchial asthma occasionally develop *tolerance* to the compound if it is repeated often. Increasingly larger doses may then be needed to give relief and these may cause marked side-effects. *Epinephrine refractoriness* is not uncommon in protracted severe cases and in status asthmaticus. Although a true tolerance develops toward the bronchial antispasmodic action of epinephrine, addiction is not observed. Psychic dependence (habituation) may occur, however, and the patient is apprehensive of the withdrawal of the drug due to fear of the return of the asthmatic attack. The use of epinephrine is reserved for the relief of acute paroxysms and other measures are employed in mild attacks or for preventive therapy.

Epinephrine may be administered in several different ways. The *aqueous solution* (1:1000) may be injected *subcutaneously.* The dose depends on the severity of the attack, the age of the patient and the response to previous therapy with epinephrine. The usual dose for adults varies from 0.2 to 0.5 cc (children, 0.1 to 0.3 cc). This may have to be repeated at 10 or 15 minute intervals until relief is afforded, benefit usually appearing within three to five minutes after the injection. Tremors and nervousness often herald the approach of cessation of the paroxysm. Because the drug impedes its own absorption from the subcutaneous tissue due to vasoconstriction, vigorous massage over the site of injection may give relief from a return of the dyspnea by promoting absorption of locally retained epinephrine. Occasionally, this procedure is effective in a lessened degree even an hour or more after the injection.

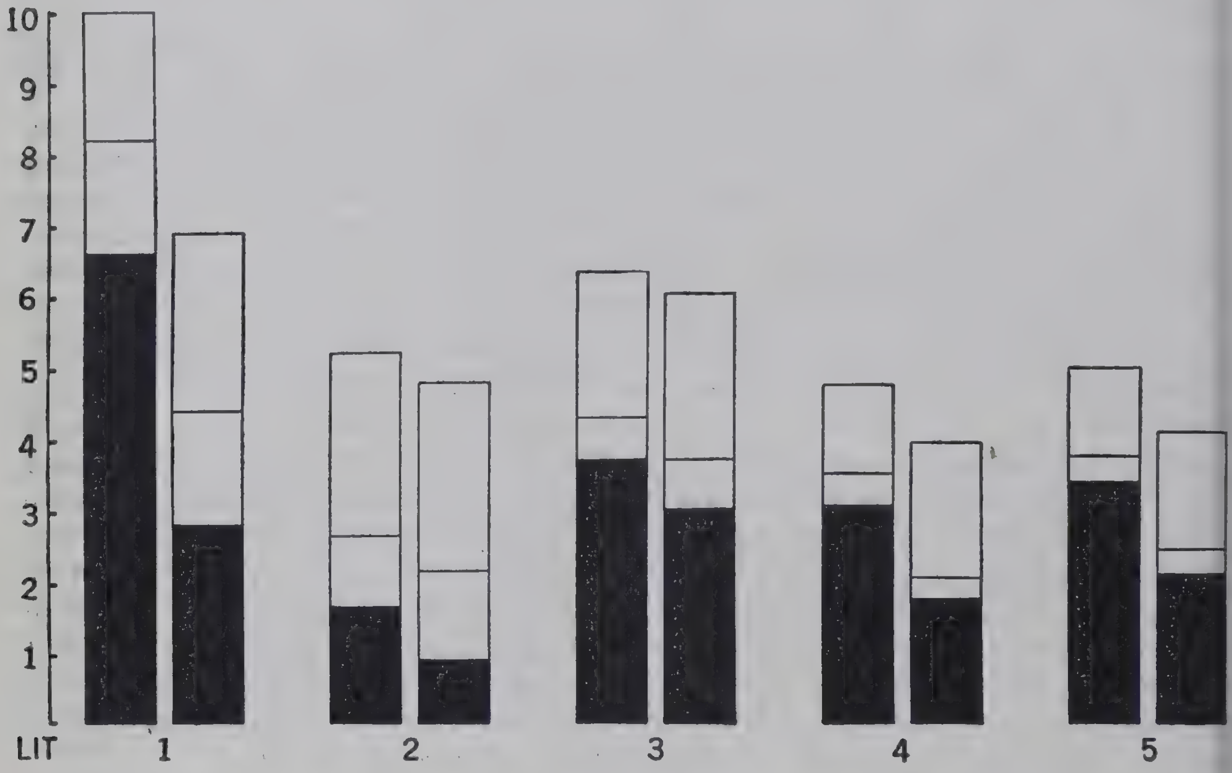


FIGURE 42. *The effect of the bronchodilating action of epinephrine on the total pulmonary capacity and its subdivisions in patients during the acute respiratory distress of bronchial asthma.*

The ordinate scale indicates volume of air in liters. Five cases are depicted, the left column in each pair indicating the status before therapy, and the right column the status soon after relief was obtained by the subcutaneous injection of 0.75 cc of a 1:1000 solution of epinephrine hydrochloride (case 4 received 0.5 cc). The black area in each column represents the residual air; the white space above is the vital capacity. The line dividing the vital capacity is the mid-capacity level. At the height of the acute asthmatic attack, there is a decrease in the absolute and relative value of the vital capacity, and a marked increase in the mid capacity and residual air. A few minutes after the administration of epinephrine, the vital capacity increases and there is a marked decrease in the mid capacity and residual air, these changes being associated with an amelioration or disappearance of the respiratory distress. (After Hurtado and Kaltreider, 1934. Courtesy of the *Journal of Clinical Investigation.*)

In patients refractory to epinephrine or in status asthmaticus, *intravenous injection* of the 1:1000 aqueous solution of epinephrine may be employed if the patient has failed to respond to the drug given by the hypodermic route. The technic is as follows: The needle is kept in the vein. After the hypodermic dose that is known not to cause unpleasant symptoms has been injected *very slowly* intravenously, additional increments of 0.05 to 0.1 cc are administered every one-quarter to one minute, according to the response of the patient, until relief is obtained. Injections may have to be continued for 15 minutes or more. Some claim that relief invariably follows this treatment. The patient then falls into a deep sleep, often his first respite in days. It would seem safer, however, to employ other measures in refractory patients, such as *theophylline, helium* and *oxygen,* rectal anesthesia with *ether in oil* or *avertin,* or intravenous anesthesia with a *barbiturate,* in order to break into the severe asthmatic cycle. Once this is accomplished, the former susceptibility to small doses of epinephrine is usually restored.

Epinephrine in oil may be employed instead of the aqueous solution (Keeney and coworkers, 1938, 1939; Murphy and Jones, 1939; and others). The suspension should be given by the intramuscular route (deltoid or gluteal) if repeated therapy is needed; otherwise it may be injected subcutaneously. In patients with acute severe paroxysms, a preliminary subcutaneous injection of the aqueous solution may be needed prior to the intramuscular therapy, due to the delayed onset of action (15 to 30 minutes) of the latter. It is useless to administer epinephrine in oil if the aqueous solution has failed to give relief. The usual dose for adults with acute asthma is 0.5 to 1.5 cc; for children, 0.25 to 0.75 cc. The dose should not be repeated until the effects of the previous injection have disappeared. The action of epinephrine in oil persists much longer than does that of the aqueous solutions. Relief lasts from four to 24 hours, usually from eight to 16 hours, whereas the aqueous solutions frequently afford relief for only one hour. Obviously the advantage of the preparation is its prolonged action due to its slow rate of absorption, as compared with the often fleeting effect of the aqueous solution which necessitates repeated injections at short intervals. The systemic responses to epinephrine in oil are also milder as well as more protracted than those to epinephrine hydrochloride solution. For example, the hyperglycemia which follows epinephrine in oil persists eight or nine hours, whereas that following the aqueous preparation, though more marked, is over in about three hours. The cardiovascular responses to the drug in oil also persist eight or nine hours, as compared with 45 to 90 minutes for epinephrine hydrochloride (Keeney, Pierce and Gay, 1939). In a series of 70 patients receiving a total of 967 injections of epinephrine in oil, Keeney (1939) observed only one severe reaction to the oil and one to the epinephrine. A 23 to 25 gauge needle should be employed to lessen the possibility of rupturing small blood vessels and thereby hastening the absorption of the solution.

Epinephrine in oil is particularly valuable in patients with *chronic asthma* who usually respond well to the preparation, experiencing fewer attacks and requiring fewer injections. A dose of one cc frequently permits an entire night's sleep free of attacks. The precautions and contraindications attending the use of epinephrine in oil are the same as those outlined previously for aqueous solutions of epinephrine hydrochloride. Keeney has reported his results in a series of individuals with chronic asthma who required from five to 10 injections of 0.3 to 0.5 cc each of the aqueous solution each 24 hours for periods varying from three months to eight years. When placed on epinephrine in oil, these patients were relieved for from eight to 16 hours by a single injection.

Epinephrine may also be administered by *inhalation* for the relief of bronchial asthma. The technic of applying the drug directly to the bronchial mucosa in asthma is not new, having been first tried by Ephraim in 1910. (*See* Graeser [1939] for historical review.) Stronger solutions than the conventional 1:1000, however, were not employed until 1935 when Graeser reported his results in asthma with a 1:100 solution. The 1.0 per cent aqueous solution of epinephrine hydrochloride is used. Weaker solutions (1:200) are less effective and a two per cent solution (1:50) rarely gives more relief than the one per cent and causes much more frequent systemic effects, such as tremor, palpitation and headache. A special *all glass* nebulizer is needed, contact with metal being avoided, and considerable practice may be required to use the apparatus skilfully. The fine spray is inhaled at the very moment the bulb of the nebulizer is compressed in order that the solution may be properly distributed in the lungs. Special inhalation masks supplied with the nebulized solution by a motor driven pump are also available and are particularly useful for children. A spray of high density and consisting of droplets of extreme fineness (mistlike) is needed for best results and many failures are traceable to disregard of these technical factors, especially the choice of a nebulizer.

A simple technic for *continuous inhalation* of vaporized bronchodilator solutions for severe asthmatic states has been reported by Richards, Barach and Cromwell (1940). It consists in the use of a pressure tank of oxygen with the usual reducing valve to regulate flow, the outflow tube being attached to the vaporizer. Oxygen is run into the vaporizer at a rate sufficient to produce adequate vaporization. A flow of four to seven liters per minute vaporizes one cc of solution in three to 10 minutes. The patient simply holds the nozzle of the vaporizer to his oropharynx and breathes quietly. The advantages of this method over the hand-bulb are that it can be employed without effort on the part of the patient (a boon to those exhausted from a severe asthmatic attack), a larger amount of solution is brought into contact with the bronchial mucous membrane, and less irritating solutions than one per cent epinephrine (*e.g.*, one per cent neo-synephrin) may be administered effectively whereas they are useless with the hand-bulb vaporizer.

Exact dosage for epinephrine by inhalation cannot be stated. Several inhalations may be required to obtain relief when the hand-bulb is employed. With the aforementioned continuous inhalation technic, a single treatment consists in the inhalation of 1.0 to 2.0 cc of solution over a period of three to 10 minutes. Relief occurs approximately as rapidly as after the subcutaneous injection of the aqueous solution and before systemic effects on the cardiovascular or nervous system are prominent. The patient should be impressed with the necessity of avoiding overdosage. Swallowing of the epinephrine solution may cause epigastric pain and the patient should therefore be instructed to rinse his mouth after using the spray. A bright pink color may be observed in the mucus expectorated after the inhalation. This is due to a change in the color of the drug and the patient should be told not to mistake this for blood. Too frequent use may result in dryness of the throat and tracheal and bronchial irritation. Inhalation therapy may then have to be suspended for several days. Graeser (1935, 1936, 1939) has had wide experience with the inhalation therapy of asthma and has observed no untoward harmful effects from it. Naturally, the course of the disease is unaltered. Inhalation of epinephrine has also been employed for the relief of angioneurotic edema. The value of inhalation over injection therapy is obvious, but therapy should be instituted only under the supervision of a physician. Further clinical experience with this method and with epinephrine in oil are required before their comparative merits will be fully known.

Miscellaneous Allergic Disorders. Epinephrine occupies an important place in the therapy of a number of miscellaneous types of acute allergic disorders. It affords symptomatic relief in many cases of *giant urticaria, serum reactions, serum sickness* and *angioneurotic edema.* When angioneurotic edema threatens suffocation due to involvement of the larynx, the drug may be life-saving. Epinephrine affords surcease from the discomfort of itching, hives, swelling of the lips, eyelids, tongue, etc., and other allergic features of the syndromes listed above. In certain forms of *eczema-dermatitis,* the drug may also give symptomatic relief. When performing *skin tests* for hypersensitiveness to various food, pollen and other allergens, epinephrine should always be at hand for the control of acute untoward responses. When the *conjunctival test for serum hypersensitivity* is employed, the discomfort of positive reactions is readily controlled by a few drops of epinephrine solution instilled in the conjunctival sac. Epinephrine in oil may be employed in small doses for the symptomatic relief of *hay fever* (Keeney, 1939).

Miscellaneous Uses. Epinephrine is of considerable value for the control of *nitritoid crises* and associated angioneurotic phenomena occurring during the course of therapy with arsphenamines. A solution of the drug ready for immediate use should be at hand during the administration of any of the arsphenamines, and an intramuscular injection of 0.5 cc should be given at the first evidence of nitritoid symptoms. This usually results in prompt relief. The onset of *inoculation malaria,* if unduly delayed, can be hastened by the intramuscular injection of 0.5 mgm of epinephrine. A similar amount may be injected in the event of a spontaneous termination of the malaria before therapy is completed. The mechanism of action is a contraction of the spleen and release into the circulation of blood containing the malarial plasmodia. In severe *hypoglycemia* due to hyperinsulinism or an overdose of insulin, epinephrine may be employed as an emergency measure to elevate the blood sugar pending the administration of carbohydrate. The drug is ineffective unless the liver contains adequate glycogen. For this reason and because the response varies considerably in different individuals, no great reliance should be placed upon the use of epinephrine in this emergency. A single subcutaneous injection of 0.5 mgm may be given but should not be repeated if ineffective. In *syncopal reactions* of the vagal and depressor variety due to *abnormal sensitivity of the carotid sinus,* epinephrine may have some beneficial effect (Weiss and associates, 1936). Other uses of epinephrine may be found by consulting the index.

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CHAPTER 24

DRUGS STIMULATING STRUCTURES INNERVATED BY ADRENERGIC NERVES (SYMPATHOMIMETIC DRUGS)

II. EPHEDRINE, BENZEDRINE AND MISCELLANEOUS SYMPATHOMIMETIC DRUGS

EPHEDRINE

Source and History. Ephedrine is an alkaloid occurring in various plants belonging to the genus *Ephedra,* a gymnosperm related to the pines and firs. The genus is indigenous to the temperate and subtropical latitudes of Europe, Asia and America, and grows especially in Northern China, Northern India and Spain. In the United States, *Ephedra* plants grow along the Rocky Mountains but most of the naturally occurring types in this country do not yield the ephedrine alkaloid. The alkaloid and its isomers exist in the stems of the plant to the extent of about one per cent, the content increasing through the spring and summer and becoming maximal just before the frosts, the old Chinese custom of collecting the plant for medicinal use in the autumn thereby being vindicated.

The Chinese herb containing ephedrine and called *Ma Huang* (yellow astringent) was employed empirically by native physicians for over 5000 years. The Emperor Shen Nung (2760 B.C.) is supposed to have tasted *Ma Huang,* as well as all other drugs in the pharmacopeia, and placed it in the "medium class." The Chinese Dispensatory (Pentsao Kang Mu) written in 1569 by Shih-Cheng Li mentions that the drug is valuable as an antipyretic, diaphoretic, circulatory stimulant and sedative for cough. Ephedrine came to be an ingredient of several favorite native prescriptions. The plant was also widely employed in Russia for many centuries, particularly for respiratory disorders and rheumatism. The Indians and Spaniards of the southwestern United States used ephedrine plants for various medicinal purposes, especially venereal diseases.

An active principle was first isolated from *Ma Huang* by Yamanashi in 1885. Nagai obtained the alkaloid in pure form two years later and named it *ephedrine.* Pharmacological investigation by Japanese workers indicated that the drug was toxic, large doses having been used. Its mydriatic properties were noted by Miura (1887), however, and as early as 1888, Takahashi and Miura concluded that the drug caused dilatation of the pupil through stimulation of the sympathetic nerves. Ephedrine then enjoyed a passing vogue as a mydriatic, several years before the isolation of epinephrine. Japanese scientists continued their investigations of the alkaloid, observed its sympathomimetic properties and employed it in the treatment of asthma.

Interest in ephedrine in Western medicine was created by the investigations of Chen and Schmidt which began in 1923 as a result of a Chinese druggist's assurance that *Ma Huang* was really a potent drug. These workers established the cardiovascular effects of the alkaloid, its similarity to epinephrine and the fact that it could be effectively absorbed from the intestinal tract (Chen and

Schmidt, 1924). Numerous clinical and experimental studies soon followed and the use of ephedrine spread so rapidly that 10 tons of the alkaloid are now consumed yearly. Synthetic ephedrine (racemic) was first prepared in 1927 and marketed under the name *ephetonin.* The details of the interesting history and pharmacognosy of ephedrine may be found in the extensive review by Chen and Schmidt (1930).

Chemistry. Ephedrine differs chemically from epinephrine in two important ways—it lacks the hydroxy groups on the benzene ring and it contains a third carbon atom on the aliphatic chain in the form of a methyl group (Table 21). These two differences account for the many properties of ephedrine which are distinct from those of epinephrine, particularly greater stability and actions on the central nervous system. The discovery of ephedrine stimulated the search for other sympathomimetic amines with three carbon aliphatic chains which would possess advantages over epinephrine, and from this search at least one important therapeutic agent has been obtained, namely, benzedrine.

Inasmuch as ephedrine contains two asymmetric carbon atoms, two sets of stereoisomers, six in all, are possible. The six have been prepared synthetically and they are designated as *l-*, *d-*, and *dl*-ephedrines and *l-*, *d-*, and *dl*-pseudoephedrines. Only two of the six alkaloids are found in the plant, however, these being *l*-ephedrine (the one official in the U.S.P.) and *d*-pseudoephedrine, and these two are more active than the other four isomers. Pseudoephedrine differs from ephedrine in physical properties and somewhat in pharmacological activity. The chemical difference lies in the relation between the -OH on the alpha and $-NHCH_3$ on the beta carbon, the groups being close to each other in ephedrine and removed from each other in pseudoephedrine.

Mechanism of Action. The earlier theories concerning the mode of action of ephedrine have been reviewed at length by Chen and Schmidt (1930). These theories antedate the newer concepts of the mediation of the nerve impulse and thus require revision to conform to the modern knowledge of the mechanisms of action of autonomic drugs. Because of the fact that ephedrine and related sympathomimetic amines resemble epinephrine so closely in their pharmacological properties, it is tempting to assume that their mechanism of action is identical with that of the hormone of the adrenal medulla, that is, that they act directly on autonomic effector cells. In the case of ephedrine, at least, this assumption cannot be so readily accepted because the drug has certain pharmacological properties which are not easily reconciled with the theory of a direct cellular action. Ephedrine differs from epinephrine in not evoking enhanced responses after cocaine or after sympathetic denervation of certain effector organs. Indeed, these two conditions may diminish the activity of ephedrine. Whereas rapidly repeated doses of epinephrine result in no diminution in the responses to the drug, the effects of ephedrine diminish with each successive dose (tachyphylaxie). Furthermore, the vasopressor action of ephedrine is not reversed by ergotoxine as is true for epinephrine, and evidence of a vasodilator component is not obtainable. Also, ephedrine does not exhibit much activity on isolated tissue (Schaumann, 1928; Burn, 1932). Finally, under certain experimental conditions, large doses of ephedrine tend to antagonize or even reverse the actions of epinephrine (Schaumann, 1928; Curtis, 1929; Burn and Tainter, 1931; Thienes and coworkers, 1934).

It is difficult to see how the many differences between the actions of ephedrine and epinephrine can be resolved by a single explanation. Nevertheless, several of them have been interpreted on the basis that ephedrine exerts an inhibiting effect on the enzyme which oxidizes epinephrine. It will be recalled that *amine oxidase* destroys epinephrine but not ephedrine (page 410), and this accounts in part for the greater stability of ephedrine in the body. Also, ephedrine inhibits amine oxidase *in vitro* (Blaschko, Richter and Schlossmann, 1937; Blaschko, 1938; Richter, 1937). Gaddum has advanced the hypothesis that ephedrine acts to inhibit amine oxidase and likens its mechanism of action to that of eserine which inhibits cholinesterase (*see* Gaddum, 1938). Thus, just as eserine protects the acetylcholine released at cholinergic nerve terminals from enzymatic destruction, so ephedrine may protect the epinephrine-like substance (sympathin) released at adrenergic terminals. Under conditions when sympathin is not released, as in denervated structures or in isolated tissue, ephedrine may not exhibit sympathomimetic properties, just as eserine is inactive under comparable circumstances. When small amounts of epinephrine are added, however, the activity of ephedrine is restored, just as the addition of acetylcholine permits eserine to manifest its activity. Indeed, the experiments of Schaumann (1928), Reinitz (1929), Koppanyi and Luckhardt (1931), Burn (1932), Pak and Tang (1933), Gaddum and Kwiatkowski (1938) and others indicate that ephedrine may potentiate the effects of epinephrine under a variety of circumstances and that when the experimental situation is such that ephedrine is inactive, the addition of minute amounts of epinephrine permits ephedrine to exhibit its characteristic actions. That ephedrine potentiates both epinephrine and adrenergic nerve impulses by protecting the hormone or sympathin from enzymatic destruction also receives support from the experiments of Gaddum and Kwiatkowski (1938). These investigators have demonstrated that low concentrations of ephedrine sensitize the isolated perfused rabbit's ear, the cat's nictitating membrane and the frog's heart not only to epinephrine but also to the stimulation of adrenergic nerves. Furthermore, the sympathin released by stimulation of adrenegric nerves was shown (by a sensitive colorimetric method) to be detectable in increased amounts in the perfusion effluent when ephedrine was present during the period of nerve stimulation.

The theory of Gaddum also attempts to elucidate the known facts that large doses of ephedrine antagonize the effects of epinephrine under certain circumstances and that rapidly repeated doses of ephedrine elicit diminishing responses. In explanation, it is assumed that ephedrine combines with the same chemical receptor substances in effector cells with which epinephrine combines, but that the former drug produces no effects when so combined with cells. The receptors thus become blocked by ephedrine so that epinephrine or sympathin cannot affect them. In other words, in high concentrations ephedrine prevents epinephrine, the substance through which it acts, from reaching effector cells.

The hypothesis presented above, in its simplest terms, claims that ephedrine acts as a substrate which combines with amine oxidase, the enzyme in the body which is presumed to destroy epinephrine, and that by successfully competing for the enzyme it protects epinephrine and prolongs its actions. Ephedrine could fill such a rôle in substrate competition because it resembles epinephrine in chemical structure but is more stable. The theory would account for the lack of activity of ephedrine on isolated and denervated structures, for the occasional antagonism between epinephrine and ephedrine and for the decrement with which ephedrine acts when its administration is rapidly repeated. However, many problems remain unsolved and more data are necessary to test the worth of the theory. Little is known concerning amine oxidase, its concentration in different loci in the body and whether it has a physiological function in connection with the organization of the adrenergic nervous system. The experimental results of Richter and Tingey (1939) questioning the ability of amine oxidase to account for the rapid *in vivo* destruction of epinephrine have already been cited (page 410). Indeed, these investigators found that the enzymatic destruction of epinephrine was not inhibited by ephedrine (in the particular concentrations employed). Nevertheless, Gaddum's suggestions are provocative and provide the basis for further experimentation from which many interesting facts may develop.

Pharmacological Actions

Ephedrine is a potent sympathomimetic agent which, in its peripheral actions, produces responses which simulate those obtained by stimulation of adrenergic nerves. Therefore, reference to Table 17 indicates, in a general way, the results to be expected from administration of the drug. Ephedrine raises the blood pressure, stimulates the heart muscle, constricts arterioles, relaxes the smooth muscle of the bronchi and gastro-intestinal tract, dilates the pupil, increases the metabolic rate, etc. In addition, however, it has a potent stimulating action on the central nervous system.

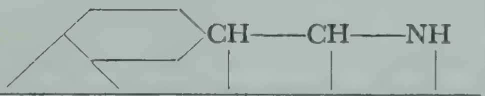
Major Pharmacological Differences Between Ephedrine and Epinephrine. The pharmacodynamic differences of academic interest between ephedrine and epinephrine have been presented under the section on mechanism of action. Certain other differences of therapeutic importance may be summarized here. Ephedrine, due to its stability, can be given by mouth. Furthermore, the duration of action of ephedrine is greater than that ordinarily obtainable with epinephrine. The constrictor effect of ephedrine on arterioles is less marked than that of epinephrine but ephedrine lacks the vasodilator component which in the case of epinephrine accounts for the fall in diastolic pressure and after-congestion. Ephedrine, repeated at too frequent intervals, may fail to exert its characteristic responses. The drug possesses a mydriatic action which makes it of value in ophthalmology. Ephedrine also stimulates the central nervous system, an action which is useful in the treatment of poisoning by central depressants and in the symptomatic therapy of narcolepsy. Finally, ephedrine exerts beneficial effects on the skeletal muscle weakness of myasthenia gravis, an action not shared by epinephrine.

Cardiovascular Actions. The effects on the cardiovascular system seen after oral or parenteral administration of ephedrine are similar to those described for epinephrine, the blood pressure being elevated, cardiac output enhanced and peripheral vessels constricted. The onset of the pressor response is slower, however, and the hypertension is much more sustained. For example, a given dose of epinephrine produces a pressor response which is from 100 to 200 times as intense as that of the same amount (by weight) of ephedrine but the effects of ephedrine persist for from seven to 10 times as long (Table 23). The compensatory bradycardia characteristically observed when epinephrine is injected intravenously in animals is less prominent in the case of ephedrine due to the fact that the hypertension develops more slowly. Even the smallest effective doses of ephedrine are vasopressor, in contradistinction to the vasodilatation caused by minute amounts of epinephrine, and a hypotensive phase does not ensue when the pressor action of ephedrine has subsided. Also, ergotoxine does not reverse the ephedrine-induced hypertension. Ephedrine acts more prominently on the heart than on the peripheral vessels, and its direct myocardial effects are the major factors in the cardiovascular responses. As stated previously, when repeated doses of ephedrine are given at frequent intervals, cardiac stimulation becomes less and less prominent and ultimately depression of the heart may occur. A possible explanation for this has been offered. The phenomenon of cardiac depression has been reviewed at length by Chen and Schmidt (1930). Very large doses of ephedrine may occasionally cause myocardial depression without much evidence of preceding stimulation. This fact enjoins caution in the use of excessive amounts of the alkaloid in patients with cardiovascular disease, and the intravenous use of the drug is not advisable.

The vasoconstrictor action of ephedrine is manifested especially on arterioles, capillaries being only slightly affected. The constriction is not as prominent as that produced by epinephrine, and thus the drug is not serviceable in local anesthetic solutions. The action is more prolonged, however, and topical application of solutions of the drug to mucous membranes results in satisfactory relief of vascular congestion unaccompanied by after-dilatation. Ephedrine acts on the *coronary* arteries in a manner similar to epinephrine, and it is likely that its predominant effect is vasodilatation. Stoland and Ginsberg (1934) found that ephedrine caused a marked and sustained increase in coronary blood flow in the intact dog. The increase was independent of a rise in blood pressure and repeated injections of the drug produced less and less effect on coronary flow. Melville (1933) found that ephedrine, like epinephrine, dilated the coronary arteries sufficiently to overcome the vasoconstriction produced by posterior pituitary extract.

TABLE 23

RELATIVE POTENCY AND DURATION OF PRESSOR ACTIVITY OF EPINEPHRINE CONGENERS *

						ACTIVITY OF EPINEPHRINE = 1	
						Pressor Activity	Duration of Pressor Action
Phenylethylamine	H	H	H	H	H	0.005–0.0125	3–4
Tyramine	OH	H	H	H	H	0.01–0.05	2
Synephrin	OH	H	OH	H	CH_3	0.01–0.04	4
Neo-synephrin	H	OH	OH	H	CH_3	0.2	2
Arterenol	OH	OH	OH	H	H	1.5	2
Epinephrine	OH	OH	OH	H	CH_3	1	1
Benzedrine	H	H	H	CH_3	H	0.002–0.01	5–10
Propadrine	H	H	OH	CH_3	H	0.003–0.017	7
Ephedrine	H	H	OH	CH_3	CH_3	0.005–0.01	7–10
Paredrinol	OH	H	H	CH_3	CH_3	0.033	10

* Modified from Gaddum (1939) and Gunn (1939).

Ephedrine, in addition to causing tachycardia, is capable of disturbing ventricular conduction and producing ventricular rhythms such as extrasystoles and fibrillation. Barbital administered beforehand provides a high degree of protection (Meek and Seevers, 1934). Arrhythmias are more rare after ephedrine, however, than after epinephrine, and it is difficult or impossible, for example, to precipitate ventricular fibrillation by injecting ephedrine in cats anesthetized with chloroform, an almost constant occurrence when epinephrine is employed. Nevertheless, in patients with serious organic heart disease or in persons receiving digitalis, ephedrine apparently can produce untoward disturbances of rhythm (Bloedorn and Dickens, 1928; Chen and Schmidt, 1930; Johnson and Gilbert, 1931; and others). Similar results have been reported in animals receiving digitalis and ephedrine (Seevers and Meek, 1935).

Cardiovascular Responses in Man. The cardiovascular responses in man observed after the administration of ephedrine were first studied by Miller (1925) who noted a rise in blood pressure in 70 of 84 individuals given 50 to 125 mgm by the oral or subcutaneous route. In seven cases, the pressure was unaltered and in six it fell. A bradycardia at the height of the rise in blood pressure was observed in the majority of persons. The hypertension persisted from six to eight hours and varied from a minimal amount to 65 mm of mercury above the control level. Similar results have been reported by many workers (*see* review by Chen and Schmidt, 1930). Subsequent investigators reported variable effects on the pulse rate, acceleration occurring in some subjects, no change or a bradycardia in others. It was also observed early that repeated administration of the drug allowed sustained elevation of the blood pressure for several days.

More elaborate studies of the cardiovascular responses to ephedrine have been made by Starr and collaborators (1937), whose results are listed in Table 22, which compares ephedrine with epinephrine. In six subjects, 50 mgm of ephedrine sulfate were injected subcutaneously and studies made at the height of action of the drug, that is, after 15 to 45 minutes. Although the subjects varied somewhat in their responses, the average results indicate a significant increase in pulse rate, systolic blood pressure, cardiac output and cardiac work. Although the pattern in the main resembles that of epinephrine, peripheral resistance is not decreased nearly so much, the heart is stimulated less, and the diastolic pressure does not fall. The elevated blood pressure is due to increased cardiac output inasmuch as peripheral resistance is diminished, the latter occurring solely as a compensatory mechanism because ephedrine lacks a vasodilator effect on blood vessels. The electrocardiograms of all but one patient showed diminution in the height of the T wave after ephedrine. One case exhibited a biphasic T wave. Changes in the electrocardiogram of subjects receiving ephedrine have been reported by others and have also been noted in animals. Patients with hyperthyroidism and essential hypertension may be more sensitive to ephedrine than normal persons, a phenomenon also observed with epinephrine.

Respiratory Effects. Ephedrine influences respiration in two ways, by dilating the bronchioles through a peripheral sympathomimetic action in a manner similar to epinephrine and by a direct stimulation of the respiratory center. Epinephrine lacks this second mechanism of affecting respiration. Respiratory stimulation from ephedrine is especially prominent when depression due to drugs is present, and thus the alkaloid is useful in the therapy of poisoning by central nervous system depressants. Even in normal subjects Starr and coworkers (1937) found that ephedrine increased respiratory minute volume by about 20 per cent (Table 22). Although experimental observations on laboratory animals seem to indicate that ephedrine is more serviceable against the respiratory depression of certain depressants (morphine) than others (phenobarbital), this difference is not evident clinically and ephedrine is one of the most useful respiratory stimulants. The antispasmodic effect of ephedrine on the bronchial muscles is less prominent but more sustained than that of epinephrine, and thus ephedrine is of value only in milder forms of asthma or in chronic cases when continued medication is needed.

Central Effects. In addition to its action on the respiratory center, ephedrine is a potent central vasomotor stimulant. The drug likewise stimulates the cortex and subcortical centers, actions which account for the insomnia, nervousness, tremor and motor restlessness occurring from overdoses and which provide the basis for the use of the drug in *narcolepsy, cataplexy* and as an *analeptic* in cases of poisoning due to anesthetics or other central depressant drugs. For example, Raginsky and Bourne (1931) found that ephedrine could shorten or interrupt avertin anesthesia in both dogs and man, and a large literature exists showing similar effects in other types of drug depression. Central stimulation produced by ephedrine also involves the spinal cord where it results in heightened spinal reflexes. Whether the efficacy of ephedrine in myasthenia gravis can be explained on the basis of its actions on the cerebrospinal axis is not known. The mechanism of the central stimulation produced by ephedrine is also unknown.

In decapitated dogs, Hinsey, Ranson and Zeiss (1931) observed that ephedrine facilitated the development of an extreme degree of resistance to passive flexion of the limbs. When properly balanced on the hind limbs, the dogs given ephedrine were able to stand and support their body weight for considerable periods of time. The animals were definitely livelier and more active reflexly than controls which were not injected with the drug. Jacobsen and Kennard (1933), employing spinal monkeys, observed that ephedrine caused an increase in the excitability of the spinal reflexes in acute preparations and hastened recovery from acute spinal "shock." In chronic preparations, ephedrine likewise caused an increase in reflex excitability. It is likely that the results of both groups of investigators are due to a direct excitatory effect of ephedrine on the spinal motor centers rather than to changes in blood supply to the spinal cord.

Actions on Smooth Muscles. The actions of ephedrine on the musculature of the blood vessels and bronchi have been discussed. The drug acts on the *iris* to cause mydriasis, an effect not generally observed after epinephrine. Mydriasis occurs both after local application of ephedrine to the conjunctiva and after systemic administration. The reflexes to light and accommodation are not abolished, cycloplegia does not ensue and the intra-ocular pressure is not altered. The drug is not serviceable in the presence of inflammation and is more effective in eyes with light-colored irides. Denervation of the pupil does not sensitize it to the mydriatic action of ephedrine, as it does to epinephrine.

The effect of ephedrine upon the *gastro-intestinal tract* is essentially one of relaxation of the musculature and inhibition of peristalsis (Gruber, 1936). The emptying time of the stomach may be appreciably delayed. Van Liere and associates (1936) observed that the oral administration to normal young adults of 65 mgm of ephedrine 20 minutes before a standard meal increased the emptying time almost twofold.

Although ephedrine acts on the musculature of the urinary bladder in a manner similar to that of epinephrine and adrenergic nerve stimulation, relaxation of the *detrusor* muscle is not prominent following administration of the drug. The tone of the *trigone* and vesical *sphincter,* however, is definitely increased. Vesical sphincter spasm has been observed as a result of the use of ephedrine, and patients receiving full therapeutic doses may complain of difficulty and discomfort in voiding. Urinary retention is particularly prone to occur in males approaching the age of prostatic hypertrophy (Boston, 1928; Balyeat and Rinkel, 1932; Valentine and Fitzgerald, 1935). The increase in vesical sphincter tone caused by ephedrine is the basis for the use of the drug in patients with nocturnal enuresis or dribbling due to poor sphincter tone. The isolated *uterus* is usually stimulated by ephedrine regardless of the response manifested to epinephrine.

Miscellaneous Actions. The effect of ephedrine on *secretions* is not prominent. *Sweating* occurs after ephedrine in man but is not demonstrable in animals. The metabolic effects of ephedrine are similar to those of epinephrine. Thus, the drug causes *hyperglycemia* but the action is not as prominent nor as constant as after epinephrine. The *metabolic rate* is increased in man (Table 22), but the response is not marked. Changes observed in the formed elements of the *blood* after administration of ephedrine are similar to those noted after epinephrine and are due to contraction of the spleen.

Absorption, Fate and Excretion. Ephedrine is adequately and readily absorbed from the intestinal tract, including the rectum. It also enters the circulation rapidly after subcutaneous or intramuscular injection. Parenterally administered ephedrine is more quickly absorbed than epinephrine, probably due to the fact that it lacks marked constrictor effect on capillaries. The fate of ephedrine in the body is unknown. The drug is not destroyed by amine oxidase, the enzyme which oxidizes epinephrine, and the resistance of ephedrine to destruction accounts for its prolonged duration of action. Thorp, Essex and Mann (1933) perfused ephedrine sulfate through heart-lung, heart-lung-limb and heart-lung-liver preparations for three hours and found that the pressor activity of the alkaloid was not diminished. Practically nothing is known concerning the excretion of the drug from the body, except that it is not rapidly eliminated by the kidneys.

Preparations. Both ephedrine and its salts are official and a variety of preparations is available.

Ephedrine, U.S.P. The official ephedrine alkaloid is levorotatory and may be obtained from *Ephedra equisetina* Bunge, *Ephedra sinica* Stapf, and other species of *Ephedra,* or produced *synthetically*. Ephedrine base is an unctuous, almost colorless solid or crystalline material. Even as the base, it is soluble in water to give an alkaline solution, and is also soluble in alcohol and liquid petrolatum, the latter becoming turbid if the ephedrine is not dry. Ephedrine base is available in the anhydrous form for the preparation of solutions in oil. Ephedrine is also marketed in N.N.R. preparations as an *inhalant* solution (one per cent in light liquid petrolatum) for application to the nasal mucous membranes, and as an *ointment* (one per cent). The N.F. contains the following preparations of ephedrine base: *Ephedrine Spray* (one per cent ephedrine and 0.2 per cent methyl salicylate in light liquid petrolatum) and *Compound Spray of Ephedrine* (one per cent ephedrine with camphor, menthol and oil of thyme in light liquid petrolatum).

Ephedrine Hydrochloride, U.S.P., B.P., and Ephedrine Sulfate, U.S.P. These two official salts are fine white, odorless crystals or powders, and are levorotatory. The hydrochloride salt is soluble 1:3 in water, the sulfate salt being freely soluble in water. Aqueous solutions are quite stable and are not decomposed by exposure to light, air or heat. The salts are available in *capsules* or *tablets* for oral use (25, 32, or 48 mgm), in *aqueous solution* (three per cent), in sterile *ampules* for hypodermic injection (25 or 50 mgm per cc) and in *hypodermic tablets* (16 and 32 mgm each). Syrups and nasal jellies are also marketed, and the N.F. contains the following preparations: *Jelly of Ephedrine Sulfate* (one per cent aqueous solution with methyl salicylate, eucalyptol, oil of dwarf pine needles, glycerin and tragacanth) and *Syrup of Ephedrine Sulfate* (containing 16 mgm per four cc dose, in syrup of cherry). The N.N.R. also includes *synthetic racemic ephedrine* (*Racĕphedrine Hydrochloride*), the actions, uses and doses of which are similar to the levorotatory salts.

Doses and Routes of Administration. The *oral route* of administration is preferred when systemic effects are sought. The usual oral dose for adults varies from 15 to 50 mgm, depending on the results desired. When chronic medication is necessary, smaller doses are usually given at three to four hour intervals. Ephedrine is ordinarily prescribed in the form of its salts and can be taken in capsules, tablets or solution. Ephedrine may also be given by *injection,* subcutaneously or intramuscularly, the dose being similar to that employed orally. Absorption from hypodermic sites, however, is not appreciably more rapid than from the intestinal tract. For *topical application* of drops or sprays to mucous membranes, solutions varying in strength from 0.5 to 3.0 per cent are used, in aqueous or oil solution, or the drug may be administered as a jelly or ointment.

For mydriasis, aqueous solutions, at least 3.0 per cent in strength, must be instilled in the conjunctival sac.

Toxic Reactions and Precautions. Most patients receiving sufficiently large doses of ephedrine experience nervousness, insomnia, tremulousness, vertigo, headache, palpitation, sweating and warmth. These symptoms, however, vary considerably in different individuals. Some patients complain of nausea, vomiting and anorexia, and precordial pain has been reported. The difficulty in urination due to vesical sphincter spasm has been mentioned. Cardiac arrhythmias may occur after ephedrine. Side-effects due to the central actions of the drug are adequately and completely counteracted by sedatives such as the barbiturates. The combined use of ephedrine and a barbiturate is sometimes resorted to in patients who are made nervous and sleepless by ephedrine when chronic medication with the latter drug is necessary. Occasionally, a patient may manifest hypersensitivity to the alkaloid and *contact dermatitis* may then occur from the topical application of its solutions.

In using ephedrine, the same precautions and contraindications should be observed as outlined for epinephrine. Special care should be exercised in using the drug in patients with organic heart disease or cardiac decompensation, hyperthyroidism, hypertension and angina pectoris, or in persons receiving digitalis. Chronic intoxication from repeated administration of ephedrine is unknown. Although some measure of tolerance may develop to the drug, addiction does not occur.

Therapeutic Uses

Ephedrine enjoys the same general field of clinical usefulness as does epinephrine, but in addition it can often be employed when epinephrine is not serviceable, due to the fact that ephedrine can be taken orally, has a longer duration of action and possesses therapeutic value as a central nervous system stimulant. Also, ephedrine is of benefit in myasthenia gravis.

Clinical Uses of Cardiovascular Actions. *Spinal Anesthesia.* The prolonged vasopressor action of ephedrine allows the drug to be employed for maintaining the blood pressure during spinal anesthesia. Ephedrine is probably the pressor agent of choice to prevent the hypotension accompanying spinal anesthesia. The fall in pressure is anticipated by the subcutaneous administration of 35 or 50 mgm of ephedrine from 30 to 45 minutes prior to anesthesia. The use of the alkaloid allows spinal anesthesia to be employed in hypertensive or hypotensive patients in whom the procedure might otherwise be contraindicated. Hypotensive subjects are sometimes resistant to the effects of the drug and should therefore be given a test dose to determine whether they are sufficiently responsive to undergo subsequent anesthesia. Ephedrine also improves the respiration, allows a better color of the skin and mucosae and lessens peripheral bleeding (Weinstein and Barron, 1936). If the blood pressure begins to fall during the course of the operation, the dose of ephedrine may be repeated. When it is necessary quickly to combat a continued fall in pressure, 25 mgm of ephedrine may be carefully injected intravenously. If this fails to check the fall, it may be necessary to resort to epinephrine.

Chronic Hypotensive States. Ephedrine offers symptomatic relief to many individuals suffering from chronic hypotensive states, especially those with *postural hypotension.* The syncopal attacks occurring in postural hypotension result from the lack of normal cardio-accelerator and vasoconstrictor responses to the assumption of the erect posture or to exercise, and ephedrine often gives striking relief. Even though the blood pressure is sometimes not markedly affected by medication with ephedrine, the patient often feels better and obtains relief from symptoms. This suggests that the improvement is due in part to central effects of the drug on the brain. Dizziness, for example, may be abolished regardless of whether the blood pressure falls to the same low level when the patient assumes a vertical position. Obviously, when neurological disease such as tabes dorsalis, syringomyelia, etc., underly the disorder, or when neurological damage has already occurred due to prolonged hypotension, the drug can offer no more than symptomatic relief. Occasionally, however, a patient is encountered who may be able to discontinue ephedrine after several months without recurrence of symptoms. The drug is given orally as often as necessary, usually 25 to 50 mgm being taken every two to four hours. The first dose each day is taken one hour before arising (Weis, 1935; Ellis and Haynes, 1936; and others).

Shock. The benefit to be obtained from the use of ephedrine in shock is neither striking nor reliable and the drug may do harm. Indeed, in the later stages of shock, ephedrine is definitely contraindicated. Large doses in particular are likely to prove injurious and myocardial depression and a further fall in blood pressure may ensue (page 588).

Complete Heart Block. Ephedrine has proved of benefit in the symptomatic therapy of complete heart block with syncopal seizures (Stokes-Adams disease). Inasmuch as chronic medication is required, the oral use of ephedrine provides a distinct advantage over the hypodermic injection of epinephrine. The minimal effective dose of ephedrine, usually 15 to 30 mgm three times daily, should be prescribed. Doses larger than necessary may have untoward effects because most patients with this syndrome have serious organic heart disease. Ephedrine accelerates the idioventricular rate and thereby removes the usual cause of the syncopal attacks. As was pointed out under epinephrine, however, it is essential to determine, if possible, the exact etiology of the syncopal seizures because ephedrine is contraindicated when transient runs of ventricular prefibrillation underlie the syndrome.

Allergic Disorders. *Bronchial Asthma.* Ephedrine gives symptomatic relief in bronchial asthma in a manner similar to that described for epinephrine, and the drug occupies a well-defined place in the management of asthmatic attacks. Inasmuch as it can be given orally and has a long duration of action, ephedrine can be used to prevent asthma. Indeed, its prophylactic value is greater than its therapeutic value. In acute severe episodes, epinephrine is the drug of choice because ephedrine is too slow in its onset of action and lacks the antispasmodic potency of the former drug. Mild attacks often yield to ephedrine and the alkaloid may abort seizures when given sufficiently early, or reduce their number and severity when given continuously. The drug seems to be more effective in allergic and reflex nasal cases than in the infectious forms of bronchial asthma. The dose ranges from 20 to 50 mgm for adults, given orally or subcutaneously as the case requires. When continued medication is used, central nervous system sedatives may be necessary to overcome the central effects of ephedrine and permit sleep.

Hay Fever. A large percentage of victims of hay fever obtain some measure of symptomatic relief from ephedrine, and a few individuals may even obtain complete relief. The drug is usually given by mouth, but a supplemental nasal spray may add to the patient's comfort. The points enumerated regarding the dosage and use of ephedrine for asthmatics also apply here. Patients who are undergoing various types of skin tests for sensitivity to specific allergens should not receive ephedrine within twelve hours before such tests because the appearance of positive reactions may be prevented.

Mucosal Congestion. In *acute coryza, vasomotor rhinitis, acute sinusitis, hay fever,* etc., ephedrine affords considerable symptomatic relief from nasal mucosal congestion and is used widely for this purpose among the laity. The long duration of action and the lack of after-congestion and intense white ischemia are distinct advantages of ephedrine over epinephrine. After topical application, the onset of vasoconstriction is rapid (few seconds to a minute) and the action on the mucosal vessels may persist for two hours or more. Whether ephedrine is contraindicated in the presence of acute infection of the nasal passages or accessory nasal sinuses is a disputed question. Some rhinologists deprecate the use of vasoconstrictor drugs and claim that such therapy removes protective hyperemia, lowers local resistance and violates the usual principles of management of acute inflammations. However this may be, no one can seriously doubt the great relief which attends the shrinkage of swollen turbinates, the re-establishment of the patency of the upper respiratory airway and the opening of blocked ostia of accessory nasal sinuses with the resulting promotion of drainage. Finally, the upper respiratory infection which characterizes the common cold is a self-limited disease, as a rule, and until it is definitely proved that topically applied vasoconstrictor agents really do harm, they undoubtedly will continue to be widely used by physicians.

The various preparations available for local application have been described. Jellies, drops or sprays may be employed, and the last two may be in oil or aqueous solution. The concentration may vary from 0.5 to 3.0 per cent. Aqueous mixtures are less irritating when they are prepared with isotonic sodium chloride solution. Nosedrops are most effectively administered when the head is in the lateral position, leaning downward (lateral head-low position) (Parkinson, 1939). The claim has been made that solutions in medicated oils may slow ciliary activity and even injure epithelium. This requires confirmation.

Mydriatic Use. The advantages of ephedrine as a mydriatic are its short duration of action and the absence of cycloplegia and increased intra-ocular pressure. It is thus especially serviceable for visualizing the fundi. A three to five per cent solution usually produces, within 30 minutes to one hour, a satisfactory pupillary dilatation which lasts several hours. Inasmuch as high concentrations of ephedrine may prove irritating, the combination of 0.1 per cent homatropine with weaker solutions of ephedrine may be employed. Pupillary dilatation without cycloplegia may be obtained by such a combination. Ephedrine may fail to exert its mydriatic effect in patients with dark-colored irides, and the drug is often ineffective in the presence of iritis or iridocyclitis.

Antidote for Drug Poisoning. Ephedrine is a useful agent in cases of poisoning by central nervous system depressants such as morphine, barbiturates, etc. It not only stimulates the medullary vasomotor and respiratory centers but it also exerts an analeptic effect on higher cerebral centers and thus tends to lessen the degree of depression. The doses of ephedrine and intervals employed depend upon the severity of the intoxication and the response of the patient. Fifty mgm may be used in adults as an initial dose, given by subcutaneous injection. The results obtained by the repeated administration of ephedrine to a patient severely poisoned by phenobarbital are diagramed in Figure 13.

Narcolepsy. The central stimulation produced by ephedrine finds an almost specific therapeutic use in the treatment of patients with narcolepsy. Ephedrine was introduced in the United States for the symptomatic relief of narcolepsy by Doyle and Daniels in 1930, simultaneously with and independently of workers in both England and Czecho-Slovakia. Ephedrine was known to produce insomnia and to counteract barbiturate anesthesia and these facts suggested its use in narcolepsy, a syndrome characterized by attacks of an irrepressible desire to sleep. The lack of detailed knowledge of the pathogenesis of narcolepsy, as well as of the physiology of normal sleep, makes it impossible to state the exact mechanism by which ephedrine acts in narcolepsy. The dose employed for adults varies from 10 to 50 mgm or more, taken orally three times daily. Small doses are used initially and increased gradually until an optimal amount is found which does not cause unpleasant side-effects. Hypertensive patients often can take the drug without the occurrence of further elevation of the blood pressure, and children tolerate the alkaloid quite well. To insure sound nocturnal sleep, which is often disturbed in narcoleptic patients, the last dose each day is administered not later than five P.M. Some degree of tolerance may develop to ephedrine after prolonged use of the drug. Although ephedrine is not a cure, it affords symptomatic relief from both the narcoleptic and cataplectic attacks which terminate entirely or are reduced in number and intensity. Sound nocturnal sleep without terrifying dreams is restored and hypnagogic hallucinations cease. Ephedrine and benzedrine are the only available sympathomimetic agents effective in this syndrome.

Myasthenia Gravis. The pathological physiology of this disease is discussed elsewhere (page 342). Before the advent of prostigmine, ephedrine represented the most useful agent for the symptomatic therapy of myasthenia gravis. Its value was discovered accidentally by Dr. Harriet Edgeworth, herself a victim of the disease, and she described the results obtained in her own case in 1930. The mechanism of action of ephedrine in increasing skeletal muscle power in myasthenia gravis is unknown. Perhaps the action of ephedrine on the cerebrospinal axis is the basis for the improvement the drug affords, although other central stimulants (except benzedrine) are ineffective. It seems unlikely that the action of ephedrine is concerned with the acetylcholine-cholinesterase system of voluntary muscles. That ephedrine, however, may act peripherally on skeletal muscle is suggested by the interesting observations of Burn (1939), who found that when fatigue occurred due to repeated stimulation of the sciatic nerve in dogs, the injection of ephedrine caused a marked rise in tension of the fatigued muscle for a prolonged period. Also, tyramine was twice as effective as ephedrine and dihydroxyphenylethylamine was twenty times as active. The effect on skeletal muscle of the last two compounds far outlasted their pressor action.

Doses of 10 to 25 mgm may be given two or three times daily; larger amounts aggravate the weakness. Some prefer to give small doses of eight milligrams at regular intervals of two hours throughout the day. The smallest effective amounts should be prescribed so that an extra dose may safely be taken in an emergency. Ephedrine appears to improve motor power of appendicular muscles more than that of muscles innervated by cranial nerves. Although some patients have been restored from complete invalidism to a normal existence by the use of ephedrine alone, the results are rarely as dramatic as those obtained with prostigmine. Ephedrine is more effective when combined with other agents. The combination of prostigmine and ephedrine is probably the most satisfactory of all the drugs of therapeutic value in myasthenia gravis. The results obtained by the use of such drug combinations have been reviewed by Viets and Schwab (1939), Schlezinger (1940), and others (page 386).

Miscellaneous Uses. In some patients with *chronic urticaria,* especially when associated with *angioneurotic edema,* ephedrine may keep the patient symptom-free and initiate periods of remission during which medication may be completely stopped. The drug may also be used to prevent *nitritoid crises,* for which purpose it is given orally in a dose of 50 mgm prior to injection of the arsphenamine. Ephedrine has also been employed to relieve the whoop in milder forms of *whooping cough.* In patients with *obstructive emphysema,* ephedrine may increase the vital capacity over 30 per cent, lower the intrapleural pressure and make breathing easier (Alexander, 1935). Good results are limited to those cases which have an abundant bronchial secretion, that is, emphysema associated with asthma or chronic bronchitis. The musculature of the smaller bronchi in such patients with abundant exudate has been found to be thickened and the mucosa hypertrophic and infected. Ephedrine presumably affords relief by decreasing the tone of the thickened bronchial muscles, thus dilating the airway. In patients with *syncopal reactions* of the vagal or depressor type due to abnormal sensitivity of the carotid sinus, therapy with ephedrine may have some beneficial effect (Weiss and coworkers, 1936). The drug has been successfully used in the treatment of *petit mal* not responding to bromides or phenobarbital. In patients with nocturnal *enuresis,* urgency and frequency of urination or poor vesical sphincter tone, ephedrine may afford symptomatic relief, presumably by increasing the tone of the trigone and internal sphincter (Valentine and Fitzgerald, 1935; Brookfield, 1937; and others). Ephedrine may be combined with belladonna for this purpose.

BENZEDRINE
(AMPHETAMINE)

Benzedrine, phenylisopropylamine, is a sympathomimetic amine which resembles ephedrine in a number of respects but differs from it chiefly in possessing greater ability to stimulate the higher centers, particularly the cortex. The initial investigations of this compound were reported by Piness, Miller and Alles (1930), Hartung and Munch (1931), Alles (1933), Alles and Prinzmetal (1933) and Tainter (1933) and it was noted early that the drug was effective after oral administration and that it had considerable pressor activity.

Piness and coworkers described the prolonged vasopressor response to benzedrine in dogs and found that when administered orally or parenterally to man, the drug caused an increase in blood pressure. Hartung and Munch also observed the pressor response to benzedrine in dogs and compared its potency with the isomeric phenylpropylamines. Alles found that benzedrine possessed about 1/100 to 1/200 the pressor potency of epinephrine but that the cardiovascular response was of longer duration, and that the drug also had bronchodilator, analeptic and respiratory stimulant properties. Alles and Prinzmetal then studied the bronchodilator activity of benzedrine in greater detail. Tainter, in an extensive examination of 44 sympathomimetic amines, observed that the pressor response to benzedrine was diminished by repeated injection of the drug or by cocaine, and that ergotamine did not reverse the rise in blood pressure. The first to employ benzedrine for its local actions on the nasal mucosa was Bertolet (1932) and the drug was accepted in 1933 for inclusion in N.N.R. as a vasoconstrictor agent for local application and inhalation in rhinology.

The marketing of the sulfate salt resulted in a rapid extension of experimental and clinical investigations of benzedrine which added to the information concerning the drug and its therapeutic uses. Unfortunately, newspaper publicity concerning the stimulant actions of benzedrine on the central nervous system led to many abuses, and numerous reports of toxic reactions caution against the lay use of the drug without medical supervision.

Chemistry and Relation of Chemical Structure to Pharmacological Actions. Benzedrine, phenylisopropylamine, is closely allied to phenylethylamine, ephedrine and propadrine in chemical structure. It differs from phenylethylamine only in having a methyl group attached to the beta carbon in the aliphatic chain. It differs from ephedrine only in that the latter has a hydroxy group on the alpha carbon and a methyl group on the amino nitrogen. Benzedrine differs from propadrine in lacking the hydroxy group on the alpha carbon. These relationships are shown in Figure 21.

The sympathomimetic properties of benzedrine reside in the benzene ring linked to an aliphatic chain containing an amino group attached to the second carbon from the ring. The pharmacological differences between benzedrine and epinephrine are due especially to the fact that the former drug possesses a three carbon aliphatic chain and lacks hydroxy groups attached to the benzene ring. The structure of benzedrine confers on it resistance to destruction and consequent effectiveness after oral ingestion and a prolonged duration of action. Its configuration likewise accounts for the marked central stimulation which the drug produces, the analeptic action being related chiefly to the three carbon chain with the amino group attached to the middle carbon and the absence of hydroxy groups on the benzene ring (Jacobsen and coworkers, 1938; Gunn, 1939).

Benzedrine exists in three forms due to the presence of an asymmetric carbon atom, the *d-*, *l-*, and *dl*-benzedrines. The dextrorotatory form appears to be from two to four times more active than the other two isomers, as determined by clinical tests in normal individuals and in patients with narcolepsy, postencephalitic Parkinson's disease and postural hypotension (Prinzmetal and Alles, 1939). The order of decreasing potency is as follows: *d*-benzedrine, *racemic* benzedrine, *l*-benzedrine. This is particularly interesting because in most instances, levorotatory compounds possess considerably more pharmacodynamic activity than the dextro or racemic isomers.

Mechanism of Action. The mechanism of the peripheral sympathomimetic actions of benzedrine is unknown. As in the case of ephedrine, it is tempting to assume that benzedrine simply acts directly on muscle and gland cells innervated by adrenergic nerves, as is true for epinephrine. Certain difficulties, however, stand in the way of such an assumption. Benzedrine differs from epinephrine in that it elicits decreasing responses as its administration is repeated (tachyphylaxis) and does not manifest enhanced activity after cocaine or on denervated structures (Tainter, 1933; Detrick and coworkers, 1937; Pinkston and coworkers, 1939). The drug is resistant to destructive deamination by the amine oxidase which oxidizes epinephrine (Blaschko and coworkers, 1937, 1938; Richter, 1937; Beyer and Skinner, 1940), being more resistant than ephedrine. Sympathomimetic amines having the structure $R \cdot CH_2 \cdot CH \cdot NH_2CH_3$ (such as benzedrine and paredrinol) are stronger inhibitors of amine oxidase than those having the structure $R \cdot CHOH \cdot CH \cdot NH_2CH_3$ (such as ephedrine). The theory of Gaddum concerning the mechanism of action of ephedrine (page 424) may eventually be shown also to apply to benzedrine, but more evidence is required, especially concerning the action of benzedrine on various denervated tissues and the effects of combined administration of benzedrine and epinephrine. In this latter connection, Pinkston and coworkers (1939) have demonstrated that benzedrine markedly potentiates the pressor response to epinephrine, a phenomenon also characteristic of ephedrine. Should Gaddum's theory apply, it would suggest that benzedrine acts through preventing the oxidation of epinephrine by amine oxidase and that the compound also competes with epinephrine for the receptor substance in effector cells.

Benzedrine also differs from epinephrine in lacking a vasodilator component.

Thus, after-dilatation does not occur, hypotension does not characterize the terminal stage of the vasopressor response to benzedrine, and ergotoxine fails to reverse the pressor action of the drug.

The mechanism of the central stimulation produced by benzedrine has not been elucidated, although the chemical basis for this action is fairly well understood. Blaschko (1940) has suggested that the ability of the sympathomimetic amines to act as analeptics *in vivo* can be directly correlated with their ability to inhibit amine oxidase *in vitro*. In line with this suggestion, the observations of Mann and Quastel (1940) are pertinent. These investigators found that the respiration of brain tissue was inhibited by certain amines such as tyramine and isoamylamine, which are oxidized to ammonia and their corresponding aldehydes by amine oxidase, the aldehydes exerting inhibitory effects on brain respiration. The addition of benzedrine increases the consumption of oxygen by the brain by binding amine oxidase so that toxic aldehydes cannot be liberated. On the other hand, benzedrine has no ability to increase the respiration of brain inhibited by anesthetic drugs, or to increase oxygen consumption of normal brain tissue. Therefore, the stimulant effect of the drug on normal and anesthetized brains remains unexplained, and it is doubtful whether the peripheral actions of benzedrine on adrenergic structures can be profitably correlated at the present time with the excitatory effects of benzedrine on the central nervous system.

Pharmacological Actions

Benzedrine shares with epinephrine and ephedrine the ability to stimulate effector organs innervated by adrenergic nerves and therefore reference to Table 17 will indicate in a general way the responses to be expected from administration of the drug. The blood pressure is elevated, peripheral vessels constricted, heart muscle stimulated, bronchial and intestinal muscles relaxed, pupils dilated, etc. In addition, like ephedrine, benzedrine stimulates the cerebrospinal axis, especially the brain stem and cortex.

Actions on the Central Nervous System. Benzedrine has the most potent action on the central nervous system of all the sympathomimetic drugs, and this property is the basis of certain unique therapeutic applications. Alles (1933), in noting that benzedrine caused a lightening of anesthesia in his experimental animals, was apparently the first to comment on the central actions of the drug. Numerous reports have subsequently appeared concerning the stimulant and analeptic properties of benzedrine. Attempts have been made to quantitate the potency of benzedrine as a central stimulant in comparison with other analeptics, especially strychnine, picrotoxin, metrazol, coramine and caffeine. The results vary depending upon the investigator, the species and doses employed, the index of recovery selected and the depressants against which benzedrine is measured (Jacobsen, 1938; Tainter, Whitsell and Dille, 1939; Chakravarti, 1939). There is little question, however, that benzedrine is a potent agent for stimulating the medullary respiratory center, lessening the degree of central depression due to anesthetic and hypnotic drugs, and stimulating the normal cerebrospinal axis. Animals receiving sufficiently large amounts of benzedrine exhibit tremors, restlessness, increased motor activity, agitation and sleeplessness to a degree not observed after ephedrine.

Central Effects in Man. Benzedrine is a potent stimulant of the central nervous system in man. The evidence for this conclusion is obtained from the clinical use of benzedrine in narcolepsy, chronic encephalitis, poisonings, etc. In 10 healthy patients, Reifenstein and Davidoff (1938) found that anesthesia produced by the intravenous injection of 0.5 gram sodium amytal was abolished by 10 to 30 mgm of benzedrine injected intravenously. Numerous studies of the *psychic* effects of benzedrine have been made (Myerson, 1936; Davidoff and Reifenstein, 1937; Nathanson, 1937; Guttmann and Sargant, 1937; Fisher, 1937; Gwynn and Yater, 1937; Bahnsen and coworkers, 1938; Jacobsen, 1939; and others). The responses produced depend upon the mental state and personality of the patient and the dose administered. The main results seen after the oral administration of 10 to 30 mgm of the drug are temporary increase in efficiency, confidence, alertness and initiative, an elevation of mood, euphoria, elation, lessened fatigue, enhanced motor and speech activity, increased ability to concentrate, irritability and sleeplessness. Several observers have reported an increase in mental performance by actual objective measurement (Sargant and Blackburn, 1936; Molitch and Eccles, 1937; Bradley, 1937), but the results of Barmack (1938) seem to indicate an increase in the desire rather than in the ability to do mental work.

The effects of benzedrine are not always as described, and many patients may complain of headache, palpitation, dizziness and vasomotor disturbances, or manifest agitation, delirium, depression or fatigue. Larger doses are always followed by fatigue and mental depression. The reversal of central effects also may follow the continued use of moderate doses. The temporary mental stimulation obtained from benzedrine in normal persons, therefore, is not always salutary, and considerable danger lies in the promiscuous use of the drug. The central effects of benzedrine bear no relation to the cardiovascular responses and are often elicited by doses smaller than those which act on the heart or blood vessels.

Respiratory Actions. Benzedrine, like ephedrine, affects respiration in two ways, by stimulating the medullary respiratory center and by dilating bronchioles. Benzedrine in animals causes a marked increase in the rate and depth of respiration through its central action (Alles, 1933; Detrick and coworkers, 1937, and others). Rapidly repeated doses elicit diminishing responses. In normal man, therapeutic amounts cause few detectable changes in respiratory rate, minute volume or vital capacity (Altschule and Iglauer, 1940). When central depression exists, however, the drug may stimulate respiration, an action which is of value in the treatment of poisoning by anesthetics and hypnotics. Although benzedrine dilates the bronchi, the effect is not marked. Clinical use of this action in asthma does not appear promising.

Cardiovascular Responses. Administered to animals in adequate doses, benzedrine causes a rise in both systolic and diastolic pressures and an increase in cardiac output and work. This is apparently accomplished by a direct action of the drug on the myocardium and a peripheral constriction of arterioles. The pulse changes are variable, but cardiac slowing secondary to carotid sinus reflexes is usually noted at the height of the pressor response. As in the case of ephedrine, repeated doses of benzedrine elicit diminishing responses and a fall in pressure may occur in some instances (Tainter, 1933; Detrick and coworkers, 1937; Pinkston and associates, 1939). The potency of benzedrine in comparison with epinephrine on a weight basis is 1:100 to 1:500 (Tainter, 1933; Alles, 1933; Detrick and coworkers, 1937) (Table 23). The cardiovascular responses of animals to benzedrine are characterized by considerable variability, a feature not noted with ephedrine. Cocaine does not potentiate the pressor response to benzedrine and ergotamine does not produce a reversal (Detrick and associates, 1937).

Effects in Man. Benzedrine also elicits variable cardiovascular responses in man, depending upon the dose and route of administration, the presence or absence of disease, and other factors. Although pressor effects may be obtained in normal persons after the oral administration of as little as 10 mgm of the drug, usually larger amounts are required. Both the systolic and diastolic pressures rise.

but this is not invariable and considerable fluctuation, especially in diastolic pressure, may occur. As in the case of ephedrine, a fall in diastolic pressure is not unusual and the pulse pressure is thereby increased. Paradoxical falls in blood pressure have also been observed and unpredictable increases or decreases in both the systolic and diastolic levels, alone or in combination, may occur. Given *subcutaneously* or *intravenously,* benzedrine is much more constant in its pressor effects. In contrast to epinephrine, therapeutic doses of benzedrine in normal subjects do not increase cardiac output or accelerate the velocity of blood flow (Altschule and Iglauer, 1940).

Myerson and coworkers (1936) observed that the subcutaneous administration of benzedrine in 18 subjects in doses of from nine to 50 mgm caused a gradual rise in systolic pressure over a period of 10 to 85 minutes, the pressure returning to normal in from one and one-half to eight hours. The rise varied from 10 to 64 mm systolic, the elevation in diastolic level being less prominent. The spinal fluid pressure increased by 25 to 40 mm of water concomitantly with the blood pressure rise (Figure 43). Alterations in pulse rate were variable, although slowing occurred in the majority of cases, and extrasystoles occasionally appeared. Oral administration of 40 mgm of benzedrine elicited roughly the same blood pressure responses as did the subcutaneous injection, but the elevation occurred more slowly. Fisher (1937) has reported that 30 to 40 mgm of benzedrine given orally to normal persons increased the systolic pressure from 20 to 30 mm of mercury, and the diastolic from 10 to 20 mm, the maximal changes occurring in about two hours and return to normal levels after four hours. The pulse rate was diminished at the height of the pressor response, but accelerated greatly on slight exertion.

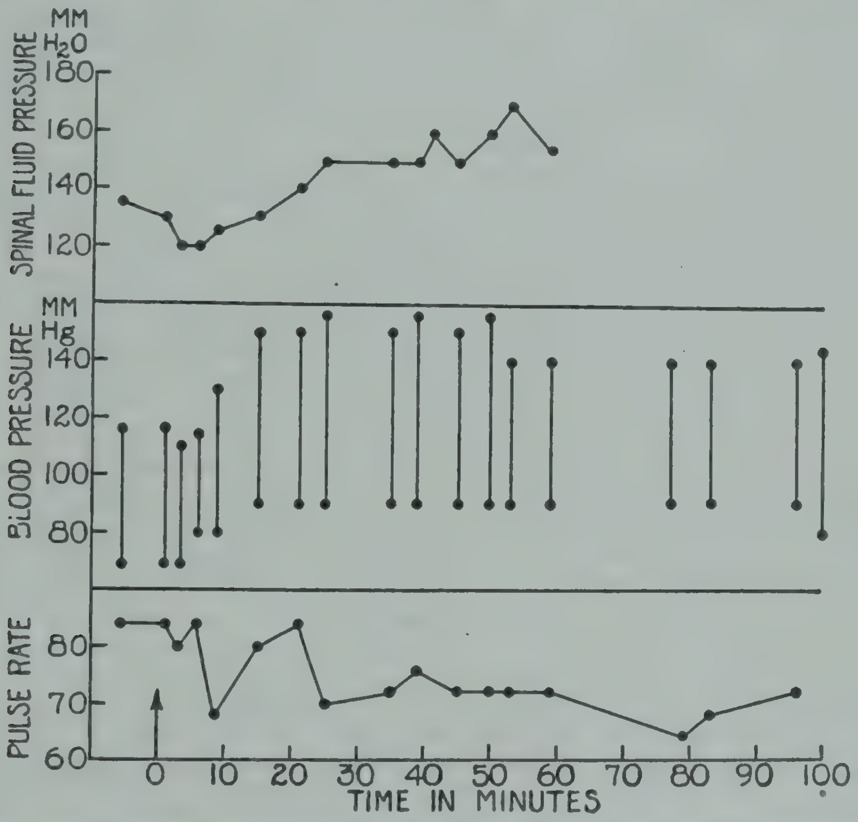


FIGURE 43. *The effect of benzedrine on the blood pressure, heart rate and cerebrospinal fluid pressure in man.*

Normal subject, basal conditions. The arrow indicates the subcutaneous injection of 20 mgm of benzedrine sulfate at zero time. The systolic and diastolic blood pressures began to rise within 10 minutes, reached a plateau at 15 minutes and remained elevated for the duration of the period of observation. The pulse rate decreased. Occasional extrasystoles were noted approximately one hour after the injection. The spinal fluid pressure rose coincident with the elevation of blood pressure. (After Myerson, Loman and Dameshek, 1936. Courtesy of the *American Journal of the Medical Sciences.*)

Anderson and Scott (1936) observed that doses of 10 to 30 mgm of benzedrine given orally caused both increases and decreases in blood pressure and pulse rate, pallor or flushing, palpitation, cardiac pain and extrasystoles. Davidoff and Reifenstein (1937, 1938) also have called attention to the many variations in cardiovascular responses after oral administration of benzedrine. Given intravenously, however, 20 to 30 mgm of the drug usually caused an elevation of 30 to 50 mm in the systolic level and 20 to 30 mm in the diastolic, the maximal elevation occurring within 30 to 60 minutes. Loman and coworkers (1939) reported that 20 to 30 mgm of benzedrine injected intravenously caused increases in blood pressure varying from 30 to 56 mm, and that normal levels were regained in from 40 to 94 minutes. Simultaneous slowing of cardiac rate was noted but arrhythmias did not occur.

Peters and Faulkner (1939) studied the effects in 10 normal subjects and 57 patients with varying types of heart disease of five deep inhalations of benzedrine (inhaler) over a period of two minutes. No significant changes were observed in the pulse rate or blood pressure and only an occasional and unimportant alteration occurred in the electrocardiogram. In only one of 28 patients with angina pectoris did the inhalations appear to precipitate an anginal attack. Dyer (1939) also studied the effects of inhalation of volatile benzedrine in 28 normal persons, 20 inhalations being taken as quickly as possible. The majority showed no change in blood pressure, the highest rise being 10 mm of mercury systolic, the greatest decrease being 15 mm. No consistent alterations in pulse rate occurred. Dyer also investigated the response to 10 to 30 mgm of the sulfate salt taken orally. The majority of individuals given 20 mgm failed to show any change in blood pressure, five of 18 subjects showing a slight elevation (10 to 20 mm) and three responding with a fall (10 mm). With 30 mgm doses, however, nine of 14 subjects exhibited a rise in pressure (10 to 35 mm). Twenty hospitalized patients with varying illnesses and degrees of hypertension were given from 10 to 20 mgm of benzedrine sulfate. Only the larger dose evoked significant changes, 10 of the 20 subjects responding with a rise (10 to 30 mm) and eight subjects manifesting a fall (10 to 25 mm). Obviously, the response to the oral administration of benzedrine is unpredictable. Hypertensive patients tend to show a fall in pressure when in poor health and confined to bed, whereas hypotensive subjects may manifest an increase in blood pressure. Only oral doses of 30 mgm or more cause significant increases in tension.

Arrhythmias of different types may occasionally occur after benzedrine, in normal patients as well as in those with heart disease. These include sinus arrhythmia, extrasystoles of auricular and ventricular origin, paroxysmal tachycardia, marked bradycardia and partial heart block. The electrocardiogram is not greatly altered in the vast majority of cases. Dameshek and coworkers (1938) observed only a slight increase or decrease in the size of the T wave. Precordial pain may occasionally be induced by the drug (Anderson and Scott, 1936).

Benzedrine applied locally to mucous membranes results in shrinkage of congested tissue due to vasoconstriction. This also occurs to a variable extent after oral ingestion, although the result is not as predictable as when ephedrine is employed. Detumescence is not followed by after-dilatation, benzedrine resembling ephedrine and differing from epinephrine in this respect.

Gastro-intestinal Tract. Considerable difference of opinion exists concerning the action of benzedrine on the gastro-intestinal tract. The results of both clinical and animal experimentation are not entirely consistent.

Beyer and Meek (1937) observed roentgenographically that benzedrine reduced by about 30 per cent the initial emptying time of the dog's stomach, but increased by about 15 per cent the final emptying time. No constant effect was detectable on the small intestine regardless of the route of administration of the drug. In a subsequent study (1939), these investigators found that toxic doses did not produce demonstrable effects on the intestine of the intact trained dog; that benzedrine increased the tonus and decreased the amplitude of contraction of the rhythmic pylorus; and that the isolated gut of the dog and rabbit responded to the drug with an increase in amplitude of contraction and decrease in tonus and rate of rhythmic activity. Other *in vitro* investigations indicate that the drug may cause either relaxation or contraction of the excised intestine depending upon the dose employed (Detrick and coworkers, 1937; Boyd, 1938).

In human beings, Meyerson and Ritvo (1936) found that the oral administration of 30 mgm of benzedrine to the average patient overcame spasm of the intestinal tract, thereby greatly facilitating roentgenographic study by making the differential diagnosis between functional spasm and organic defects more certain and giving better visualization of organic lesions. The antispasmodic action reached its height in 15 to 30 minutes, decreased within an hour and gradually disappeared. The drug was also found of value in pylorospasm and spastic colitis. Ritvo (1936) confirmed these results and noted that although the tone of the stomach was decreased by benzedrine, gastric peristalsis was diminished only slightly. The colon became widened, the haustra diminishing in number and prominence, and spastic deformities of the bowel disappeared. Opaque enemas were retained with greater ease by patients receiving benzedrine. Smith and Chamberlin (1937) studied the effect of 20 to 30 mgm of benzedrine given orally or subcutaneously in 28 subjects, including normal individuals and patients having peptic ulcer, spastic colitis or other gastro-intestinal disturbances. They confirmed the findings of the aforementioned workers in that peristalsis in the normal stomach was apparently unaffected and that inhibition may occur in patients with duodenal ulcer. In two patients with gastric atony, gastric tone was increased. The emptying time of the stomach was delayed and the motility of the small intestine diminished. Relaxation of a spastic colon during the administration of a barium enema was also promoted, thus facilitating filling and relieving the patient's discomfort. Occasionally, peristaltic rushes and to-and-fro churning in the small intestine were seen. Van Liere and Sleeth (1938) observed a 20 to 35 per cent decrease in gastric emptying time following the administration of 30 mgm of benzedrine to three normal subjects.

Rosenberg and coworkers (1938) could demonstrate no improvement in 14 of 18 patients with spastic irritable colons who were given benzedrine medication for varying periods of time. In two normal persons, the drug caused pylorospasm and enterospasm and the emptying time of the stomach and small intestine was prolonged. Similar results were obtained in dogs. Beyer and Meek (1939) found that 30 mgm of benzedrine given orally to 10 normal subjects before a test meal caused a decrease of approximately 40 per cent in the time for initial gastric emptying but an increase of about 20 per cent in the time for final emptying, results similar to their animal experiments quoted. Beyer and Meek concluded that the more rapid initial gastric emptying is due to an increase in gastric tonus and intragastric pressure, so that the contents are forced through the pylorus despite the increased tone of that structure. The final delay is due to secondary inhibition of the stomach and possibly to increased pyloric tone. Any value noted for benzedrine in overcoming pylorospasm of moderate degree is thought by these workers to be due to the initial increase in gastric tone overcoming pyloric resistance rather than to a direct inhibitory effect of the drug on pyloric tonus.

In *summary,* it may be stated that the actions of benzedrine on the gastro-intestinal tract cannot be predicted on the basis of the sympathomimetic properties of the drug, and depend on the functional level of activity at the time of drug administration. Apparently the normal stomach is first stimulated so that initial emptying is hastened but later inhibited so that final emptying is delayed. The pylorus usually manifests increased tone. It is possible, however, that paradoxical relaxation may occur in spastic states. The action of benzedrine on the small bowel is uncertain and unpredictable, but the spastic colon at times may be relaxed by the drug, especially when stimuli tending to increase spasm are present, as during the administration of a barium enema. Gastric acidity is not appreciably influenced by benzedrine. Patients receiving the drug may complain of belching, flatulence, anorexia, nausea, abdominal cramps and an increase or decrease in bowel movements. Diarrhea or constipation may also occur.

Pupillary Actions. Benzedrine is a mydriatic when instilled in the conjunctival sac. A one per cent solution causes complete pupillary dilatation in from one-half to one hour, the effect wearing off in less than two hours. The advantages of benzedrine as a mydriatic are that no significant change occurs in intra-ocular pressure, accommodation is not affected and the pupil returns to normal within a short time. Unless benzedrine is repeatedly administered, the light reflex is not lost. Benzedrine and atropine or homatropine employed together in proportionately reduced amounts allow more rapid mydriasis and cycloplegia than is otherwise obtainable and permit recovery to occur much sooner than when the belladonna alkaloids are used alone. For example, an instillation of a five per cent homatropine solution, followed in two or three minutes by a one per cent benzedrine solution, and then in turn by a second instillation of homatropine results in a cycloplegia which reaches a peak in from 50 to 70 minutes and which lasts only a few hours. If a one per cent atropine solution is employed instead of the homatropine, two to four days are required before the patient is again able to read (Myerson and Thau, 1937; Beach and McAdams, 1938; Powell and Hyde, 1938; Mayer, 1939). Myerson and Thau (1937, 1938) noted the interesting fact that benzedrine solution promotes the reappearance of the reaction to light in patients with Argyll-Robertson pupils. The explanation for this is not evident.

Actions on Other Smooth Muscles. The *biliary tract* in human beings is not greatly influenced by benzedrine. Schube and associates (1937, 1939) observed that the drug did not prevent the gall bladder from emptying normally in response to a fat meal given one-half hour after benzedrine. If the drug was administered two hours before the fat meal, however, emptying was prevented. The mechanism of this delayed effect of the drug on the gall·bladder is not clear. At no time was contraction of the viscus observed. Smith and Chamberlin (1937) observed neither stimulation nor inhibition of the gall bladder in their investigations mentioned previously, but they did not study the effect of a fat meal given late after the drug. In cats, Flexner and associates (1938) observed that benzedrine relaxed the gall bladder spasm induced by acetyl-β-methylcholine.

The *detrusor muscle* of the urinary bladder is relaxed by benzedrine and the trigone and sphincter muscles are contracted. Dysuria, frequency and urgency have been reported to occur after the drug. Loman and coworkers (1938), employing intravenous urographic technic, observed that 20 mgm of benzedrine given intravenously caused enlargement of the *kidneys* with an increase in their general visibility, dilatation of the renal pelvis and calyces, relaxation and increase in size of the *ureters,* and marked enlargement of the *urinary bladder* so that it gave the appearance of a cord bladder. These effects are exactly opposite to those noted after acetyl-β-methylcholine.

The *uterus* appears to be contracted by benzedrine. Gunn and coworkers (1939) found that the drug produced contraction of the uterus in all animals, including the non-pregnant cat, benzedrine differing in this respect from epinephrine and resembling ephedrine. Boyd (1938) recorded contraction of the isolated virgin guinea pig uterus after benzedrine.

Metabolic Effects. According to a number of clinical reports, the basal metabolic rate in man does not change appreciably after single doses of benzedrine or after continued medication. In carefully controlled experiments, however, Dill, Johnson and Daly, (1939) studied the metabolic responses to the intramuscular injection of therapeutic doses of epinephrine and benzedrine in man, and found that benzedrine had a definite calorigenic action, smaller than that of epinephrine but more sustained. These investigators noted that epinephrine did not change or slightly increased the proportion of carbohydrate utilized during the period in which the blood sugar and lactate were elevated, acetone bodies in the blood and urine fluctuating within the normal range. Benzedrine, on the other hand, did not modify carbohydrate utilization or the concentration of sugar, lactate or acetone bodies in the blood. The inability of benzedrine to elevate the blood sugar has been verified by several observers. Beyer (1939) reported a small increase in the basal metabolic rate (approximately 15 per cent) in normal human subjects given 30 mgm of benzedrine by mouth. The increase occurred within two and one-half hours and was still noted after nine hours, but the rate returned to normal within 24 hours. In contrast, Altschule and Iglauer (1940) observed that benzedrine given in doses of 10 to 30 mgm orally to 12 normal subjects caused the basal metabolic rate to rise in only two instances, cases in which the increase was attributable to restlessness caused by the drug. Clearly, the rise in basal metabolic rate caused by benzedrine is not constant or significant when compared to that produced by epinephrine.

Miscellaneous Actions. The vascular actions of benzedrine may result in changes in the *skin,* including pallor, flushing, urticaria, dermatographia and paresthesias. Excessive *sweating* may be observed in some patients. Hyperactive *carotid sinus reflexes* are diminished by benzedrine which is thus capable of preventing syncope of the vagal or depressor type (Robinson, 1937, 1938). The *deep reflexes* may be increased by the drug, and the *skeletal muscle* weakness in myasthenia gravis is improved. Changes observed in the formed elements of the *blood* are transient and probably due to the action of benzedrine on the spleen and other blood reservoirs (Pinkston and Pinkston, 1939). Continued administration of the drug does not result in permanent alteration in the blood picture (Schube and coworkers, 1937). The *spinal fluid pressure* rises moderately when benzedrine elevates the blood pressure (Figure 43).

Absorption, Fate and Excretion. *Absorption.* Salts of benzedrine are absorbed adequately and readily from the intestinal tract and from parenteral sites of administration. When benzedrine or its volatile carbonate salt is inhaled in therapeutic amounts for local effects, significant systemic actions are rarely noted.

Fate and Excretion. Benzedrine is quite stable in the body and resists destructive deamination by amine oxidase, this fact accounting for its prolonged duration of action. Benzedrine is even more stable than ephedrine and is excreted slowly by the kidney. In man, excretion begins within three hours after oral administration, and an average of 43 per cent appears in the urine within 48 hours. Obviously, the period of sojourn of the drug in the body outlasts the duration of its action. A large amount of benzedrine apparently is detoxified in the organism. In dogs with liver injury produced by carbon tetrachloride, twice the normal amount of ingested benzedrine is excreted in the urine, suggesting that the liver is the organ which inactivates the compound (Beyer and Skinner, 1940).

Preparations. Benzedrine is available in the form of its sulfate salt for oral administration and for the preparation of solutions, and as the alkaloidal base in inhalers or solution for local use on the mucosa of the upper respiratory tract. The drug is not official, but is included in N.N.R.

Benzedrine, N.N.R. This is the racemic base, a colorless, volatile liquid possessing a strong basic odor and a burning taste. It is soluble in ether, alcohol and liquid petrolatum and is slightly soluble in water. When exposed to air, benzedrine changes to its carbonate salt, which is also volatile. Benzedrine base is available as *Benzedrine Inhaler,* N.N.R., and *Benzedrine Solution,* N.N.R. Each inhaler tube contains, at the time of packing, 0.325 gram of benzedrine, 0.097 gram of oil of lavender and 0.032 gram of menthol. Benzedrine solution is marketed as a one per cent solution in liquid petrolatum perfumed with oil of lavender.

Benzedrine Sulfate (Amphetamine Sulfate), N.N.R. The sulfate salt of benzedrine is not volatile. It is a white odorless powder, freely soluble in water to yield solutions neutral to litmus, and is slightly soluble in alcohol. It is marketed in tablets, each containing 10 mgm of the drug. Benzedrine sulfate is also available as a powder for use in preparing solutions.

Routes of Administration and Doses. *Local Application.* One per cent aqueous solutions of benzedrine sulfate may be instilled in the conjunctival sac for producing dilatation of the pupil. A one per cent solution of benzedrine base in oil may be used in the form of drops or as a spray for shrinking the mucous membranes of the upper respiratory tract. The inhaler is also employed for this purpose. The amount of drug actually inhaled by the use of the benzedrine inhaler has been determined by Simpson and Simon (1937) who found that an average of 21 inhalations were necessary to supply one mgm of the drug. If four inhalations constitute an average treatment, the amount inhaled is only 0.2 mgm. If 20 treatments are employed daily, only four mgm of benzedrine are inhaled. Even if absorption were complete, this would constitute only one-fourth of the single therapeutic dose by the oral route.

Oral. Benzedrine is administered orally as the sulfate salt in tablet form. The average dose for adults varies between 10 and 30 mgm, depending on the result to be obtained. The effects of the drug appear within 30 minutes to one hour. When chronic medication is employed, the single dose is usually 10 mgm, repeated three or four times daily, but larger amounts may be necessary. In order to establish the patient's sensitivity to the drug, five mgm may be given as an initial test dose. Amounts even smaller than this may produce definite cerebral effects.

Subcutaneous. For parenteral injection, the subcutaneous route is preferred. Vascular effects appear within five minutes. The amount administered is determined by the result desired. The usual dose is 10 mgm of the sulfate salt. Intravenous injection is not recommended.

Toxicity. Toxic effects produced by benzedrine are usually extensions of the therapeutic actions of the drug and, as a rule, result from overdosage. Individuals vary in their reactions to benzedrine, and disease also alters susceptibility to the drug. Occasionally, small doses may elicit alarming symptoms due to idiosyncrasy. Most prominent among the toxic effects are the cerebral symptoms. Restlessness, tremors, insomnia, talkativeness and irritability are common. Confusion, assaultiveness, hallucinations, delirium, panic states and suicidal or homicidal tendencies have also been observed, especially in mentally ill patients. Fatigue and depression usually follow the central stimulation. The untoward effects on the gastro-intestinal tract include dry mouth, metallic taste, anorexia, nausea, vomiting and diarrhea. Cardiovascular reactions include chilliness, sweating, palpitation, marked hypertension or hypotension, extrasystoles and other arrhythmias, anginal pain, circulatory collapse and syncope.

Waud (1938) described in detail the effects of prolonged inhalation of benzedrine. In his experiments, the subject breathed through benzedrine inhaler tubes continuously from four to six hours, on eight separate occasions at weekly intervals, probably absorbing many times the usual single therapeutic dose. The chief effects noted were hypertension lasting for four days after each experiment, anorexia and marked loss of weight, mental stimulation including euphoria and increased libido followed by fatigue and depression, diuresis, increased reflexes, and orthostatic hypotension and marked emphysema following the inhalation. Permanent organic changes were not observed and the conclusion was reached that benzedrine has a wide margin of safety in normal persons. Isolated instances of severe reactions to benzedrine have been reported by several investigators. These reactions include convulsions, circulatory collapse and coma in a patient taking 140 mgm with suicidal intent (Apfelberg, 1938), panic in a student three hours after ingesting 30 mgm (Ulrich, 1937) and clonic convulsions and unconsciousness in a patient nine hours after taking 30 mgm (Smith and Chamberlin, 1937). A case of collapse and death possibly due to benzedrine was reported by Smith (1939).

Precautions and Contraindications. Foremost among the precautions to be observed in the employment of benzedrine is to discourage its abuse by the laity as a means of overcoming sleepiness or providing increased energy and alertness.

The Council has voiced the following warning in regard to this abuse (*see* N.N.R., 1940): "Its use is not recommended in the treatment of sleepiness and fatigue in normal individuals because of the possible danger of pressor effects from continued use, because of the dangers of eliminating the warning signal of sleepiness in individuals who are overdoing, because of the possibility of habit formation or addiction from such use and because cases of collapse have ensued when the drug has been used for this purpose. Its use is not recommended for developing a sense of increased energy or capacity for work, or a feeling of exhilaration or as a 'pick-me-up' in individuals other than those under the strict supervision of the physician."

Contraindications to the use of benzedrine are similar to those outlined for ephedrine and epinephrine, and include hypertension, advanced arteriosclerosis, coronary artery disease, states of mental excitement, agitated depression, hyperthyroidism and idiosyncrasy to the drug. Benzedrine should be used with caution in patients with anorexia, insomnia, vasomotor instability, asthenia, psychopathic personalities and history of homicidal or suicidal tendencies.

Habituation to benzedrine may occur in certain patients, and is somewhat similar to the habit formation produced by caffeine and nicotine, but *addiction* in the strict sense of the word is unknown. Several investigators reported an increased tolerance to the drug after continued use, but the majority of patients show no significant change in susceptibility to benzedrine during the course of chronic medication. Bloomberg (1940) reported three cases of narcolepsy in which large doses of benzedrine sulfate (70 mgm or more) were given daily for over two years without any evidence of addiction, habit formation, or deviation from the normal detectable by clinical or laboratory examination.

Therapeutic Uses

In regard to its peripheral sympathomimetic actions, benzedrine has the same general field of usefulness as have epinephrine and ephedrine. Because of its weak bronchodilator activity the drug does not seem to be of value in asthma. It shares with ephedrine the ability to benefit patients with narcolepsy and myasthenia gravis, but in addition it is of value in the symptomatic therapy of certain nervous and mental diseases.

Therapeutic Applications of the Central Actions. *Narcolepsy.* Benzedrine has been found of definite value in the symptomatic therapy of narcolepsy. Prinzmetal and Bloomberg (1935) were the first to record this use of the drug, and several reports have appeared since then (Ulrich, Trapp and Vidgoff, 1936; Davidoff, 1936; Ulrich, 1937; Nathanson, 1937; Solomon and coworkers, 1937; and others). Nearly 100 per cent of narcoleptic patients are completely relieved by benzedrine of attacks of sleep, and cataplexy is greatly improved. Bloomberg (1937) reported a series of 35 cases in which he obtained highly satisfactory results. Benzedrine has proved effective in cases in which ephedrine in large doses failed to give relief. Continued medication over prolonged periods does not seem to result in decreased effectiveness. The dose varies from 10 to 30 mgm, taken orally one to three times daily. The last dose should be given in the afternoon in order not to interfere with nocturnal sleep.

Postencephalitic Parkinsonism. Benzedrine is a valuable adjuvant to the belladonna alkaloids in the symptomatic therapy of postencephalitic parkinsonism. Solomon and Prinzmetal (1936) were the first to employ benzedrine in chronic encephalitis and later (1937) they described their results in a series of 18 patients in which the drug proved beneficial. Since then numerous similar reports have appeared (Davidoff, 1936; Bloomberg, 1937; Matthews, 1938; Davis and Stewart, 1938; Finkelman and Shapiro, 1937; and others). Although some patients are benefited by benzedrine alone, the drug is most beneficial when used with the belladonna alkaloids. In conjunction with atropine, scopolamine or stramonium, benzedrine allows a better sleep cycle, increased energy, subjective improvement in muscle strength and rigidity, a feeling of increased energy, and relief from oculogyric crises. About 85 per cent of patients manifest improvement after benzedrine therapy, and a higher percentage obtain relief from oculogyric crises, for which the drug appears to be almost specific, the attacks being reduced in number and severity or disappearing. Arteriosclerotic parkinsonism is rarely aided by benzedrine and patients with psychotic states accompanying the syndrome are not always favorably affected (Reznikoff, 1939; Reifenstein and Davidoff, 1939). Best results are noted when the disease is postencephalitic in origin and when organic defects and personality changes are minimal. Subjective improvement is greater than objective decrease in tremor and rigidity. The dose employed varies from 10 to 100 mgm or more daily, taken in divided portions.

Alcoholism. In cases of chronic alcoholic addiction, benzedrine occasionally proves of benefit in assisting patients to abstain from alcohol. Fourteen of the 21 cases reported by Bloomberg (1939) appeared to be helped by benzedrine medication. The drug has also been employed as a stimulant in acute alcoholic stupor and may shorten the period of recovery from intoxication. Reifenstein and Davidoff (1940) recorded that nearly all of their patients with acute psychosis due to alcoholism showed accelerated recovery in response to benzedrine, the best results being obtained in cases of recent origin. Mild states of depression following drinking debauches were also benefited. Unsatisfactory results were obtained in chronic alcoholic addiction without psychosis. More experience is required before the indications for and dangers of the use of benzedrine in alcoholism can be evaluated.

Psychogenic Disorders. Benzedrine has been employed in a variety of mental diseases and a large and controversial literature is accumulating concerning its value. It has been used in mild mental disorders such as mood disturbances, chronic nervous exhaustion and psychoneuroses, as well as in major psychoses such as dementia praecox and the depressed form of manic depressive psychosis. The immediate results are quite good in cases of depression and chronic exhaustion and in some instances improvement may be spectacular. The results are not striking in psychoneuroses, and anxiety states may be aggravated. Patients with involutional melancholia do not respond well. Some evidence exists that benzedrine accelerates improvement in patients with the depressed type of manic depressive psychosis and also in certain patients with dementia praecox (Reifenstein and Davidoff, 1939). Wider investigations are required before the value and dangers of benzedrine in psychogenic disorders will be known. Whether it is safe and logical continuously to stimulate individuals with mental disturbances is unknown, and the indiscriminate use of benzedrine in patients with psychic disorders cannot be too severely criticized. (*See* Wilbur and associates, 1937; Nathanson, 1937; Schube and associates, 1937; Solomon and coworkers, 1937; and the review by Reifenstein and Davidoff, 1939.)

Drug Intoxication. Benzedrine has not received extensive trial as an analeptic in cases of poisoning by central nervous system depressants. Although it is capable of lessening the degree of depression produced by anesthetics and hypnotics, benzedrine lacks the potent respiratory stimulant action of caffeine and ephedrine, and thus cannot be relied upon alone. In conjunction with other measures, however, it may prove useful in poisoning by depressant drugs. Boyd (1940) has reported on the use of benzedrine to shorten the period of postoperative unconsciousness following avertin anesthesia in children.

Therapeutic Application of the Cardiovascular Actions. *Local Vasoconstriction.* Benzedrine in the form of the inhaler or solution in oil serves the same purpose as does ephedrine in the treatment of congestion of the upper respiratory mucosa. It is thus widely employed in *hay fever, acute coryza, acute sinusitis, vasomotor rhinitis,* etc.

Orthostatic Hypotension. Benzedrine has received therapeutic trial in orthostatic hypotension where the results appear to be as good as those obtainable with ephedrine. The dose may vary from 50 to 150 mgm daily, given orally in divided portions, the first dose of 25 mgm to be taken one-half hour before arising. Smaller amounts are taken during the day at such intervals as may be necessary to prevent symptoms (*see* Davis and Shumway-Davis, 1937; Korns and Randall, 1937, 1938).

Miscellaneous Uses. Benzedrine is useful in ophthalmological work as a *mydriatic,* for which purpose a one per cent aqueous solution is employed. The advantages of benzedrine and the technic of combining it with the belladonna alkaloids have been described. In patients with *syncope* due to abnormal carotid sinus reflexes, benzedrine decreases the number and severity of attacks (Robinson, 1937, 1938). In *myasthenia gravis,* Thorner and coworkers (1937) found benzedrine advantageous in three of five cases. The mechanism of action of benzedrine is increasing skeletal muscle power in myasthenia gravis is unknown. It probably is identical with that of ephedrine. In *persistent hiccough,* the administration of benzedrine has been reported to check the attacks (Shaine, 1938; Hanelin, 1939). The mechanism of action is not clear. The equivocal *antispasmodic action* of benzedrine on the gastro-intestinal tract has been described. Although the drug may occasionally be beneficial to patients with spastic colitis and may prove useful in roentgenological diagnosis, it lacks the general antispasmodic usefulness of the belladonna alkaloids and their synthetic substitutes. Benzedrine has also been reported to be beneficial in the treatment of *enuresis* in children (Molitch and Poliakoff, 1937) and in *migraine* (Nathanson, 1937). In *epilepsy,* benzedrine is valuable as an adjuvant to phenobarbital, correcting the ataxia and drowsiness produced by the sedative and allowing sufficient amounts of phenobarbital to be employed to control convulsive seizures (Cohen and coworkers, 1940; Ebaugh, 1940; and others).

NEO-SYNEPHRIN

Neo-synephrin is a synthetic, optically active sympathomimetic amine which differs from epinephrine chemically only in that it has one rather than two hydroxy groups on the benzene ring. The hydroxy group is placed in the position meta to the aliphatic side chain (Table 21). Barger and Dale (1910) studied the pharmacological actions of monohydroxy benzene sympathomimetic amines and concluded that meta- and para-hydroxy compounds were equally effective. It was later determined, however, that in the case of monohydroxy derivatives the meta position afforded optimal activity and neo-synephrin replaced an older preparation, *synephrin,* in which the hydroxy was in the para position. In addition, synephrin was a racemic compound and this also reduced its activity.

Pharmacological Actions. The pharmacological actions of neo-synephrin are similar to those of epinephrine. Thus the compound raises the blood pressure by peripheral vasoconstriction and cardiac stimulation. The effect on the heart is less than that of epinephrine and compensatory reflexes (or possibly a direct depression of the S-A node [Keys and Violante, 1940]) slow the heart rate to below normal. Accompanying the bradycardia are an increase in heart size and stroke volume (Keys and Violante, 1940). Cardiac arrhythmias are much less likely to occur than after epinephrine. In contrast to epinephrine, the incidence of untoward reactions from neo-synephrin, such as anxiety, tremor, nervousness, and headache, is low. Lastly, neo-synephrin is much more stable and produces more lasting responses than does epinephrine. After intravenous administration of the compound, the blood pressure remains elevated for approximately 15 minutes, and after subcutaneous or intramuscular injection, one hour to two hours or more. The stability of neo-synephrin allows the drug to be taken orally. After administration of neo-synephrin by mouth, bronchodilatation as well as cardiovascular responses can be observed.

Routes of Administration and Dosage. Neo-synephrin can be given intravenously, intramuscularly, subcutaneously or orally. The intravenous dose is 0.5 mgm; the subcutaneous or intramuscular, approximately five mgm. Adequate pressor effects are obtained after the oral administration of 20 to 50 mgm. For topical application to mucous membranes, a solution of 0.25 per cent is usually employed and for combination with local anesthetics a concentration of 1:5000 is sufficient.

Preparations. *Neo-Synephrin Hydrochloride,* N.N.R., is a white crystalline powder readily soluble in water. It is marketed for topical application as a 0.25 or 1.0 per cent aqueous solution with 0.8 per cent sodium chloride and 0.1 per cent sodium benzoate; for parenteral administration, as a 1.0 per cent sterile isotonic solution. It is also dispensed in a jelly base in 0.5 per cent strength and as a 0.25 per cent emulsion in mineral oil containing camphor, menthol and oil of thyme. Neo-synephrin is stable and resists decomposition by boiling, exposure to light and air, and contact with alkaline solutions.

Therapeutic Uses. Neo-synephrin is extensively employed for *topical application* to nasal mucous membranes for the symptomatic relief of *sinusitis, vasomotor rhinitis* or *hay fever.* It is a suitable agent for *sustaining the blood pressure* during *spinal anesthesia,* being superior to ephedrine in that it does not affect the central nervous system and does not lose its efficacy as a pressor agent upon repeated administration. For this purpose, five mgm may be injected subcutaneously and repeated if necessary (Bittrich, 1939; Brunner and Takats, 1939; Lorhan and Lalich, 1940). It is also employed in a concentration of approximately 1:5000 in solutions of local anesthetics as a *vasoconstrictor agent.* Capaccio and Donald (1938) report an interesting case of *orthostatic hypotension* in which neo-synephrin afforded complete symptomatic relief after ephedrine and benzedrine had proved ineffective. The dose initially employed was 50 mgm by mouth every two hours, but this was soon reduced to 20 mgm, taken three times during the morning.

PROPADRINE

Propadrine is a sympathomimetic amine with actions similar to those of ephedrine. It differs chemically from ephedrine only in that it lacks a methyl group on the amino nitrogen. Its chemical structure is presented in Table 21. The compound was first investigated by Chen and associates (1929) in connection with a series of sympathomimetic amines chemically related to ephedrine. They observed that it had a somewhat greater pressor activity than ephedrine. Clinical reports on the drug reveal that it is less likely than ephedrine and benzedrine to cause central stimulation.

Propadrine Hydrochloride, N.N.R., is a white, crystalline, water-soluble powder. It is marketed in capsules containing 25 or 50 mgm, as a *nasal jelly* containing 0.66 per cent of the drug, and in *aqueous solution* (one and three per cent). The therapeutic indications for propadrine are essentially the same as those for ephedrine, and it may be employed in approximately the same dosage.

KEPHRINE

Kephrine is a sympathomimetic amine which differs from epinephrine in that it has a keto rather than a hydroxy group on the aliphatic side-chain. Its structure is presented in Table 21. Kephrine was studied early in the course of investigations of compounds chemically related to epinephrine and was included in the series investigated by Barger and Dale (1910). At that time it was noted that the keto derivative was less active than epinephrine but that its action was more sustained.

Kephrine Hydrochloride, N.N.R., is a white, water-soluble, crystalline powder. It is employed in therapeutics only for its local action as a hemostatic. It is marketed in *powder form* (diluted to five per cent concentration with tricalcium phosphate), in *rectal suppositories* (containing three parts of kephrine hydrochloride and one part of extract of belladonna in 96 parts of base), and in *impregnated bandage or gauze* (3000 square centimeters being impregnated with one gram of kephrine hydrochloride).

PAREDRINE

Paredrine is a sympathomimetic amine which was first synthesized and patented in Germany in 1913. The compound excited little attention at that time and was not reinvestigated until Alles (1933) studied the pharmacological actions of a series of sympathomimetic amines of which paredrine was one. Shortly thereafter, the compound became commercially available and soon there followed a series of publications on its effects in man and its clinical applicability.

Chemistry. The chemical structure of paredrine and its relation to other sympathomimetic agents are shown in Table 21. The drug is closely related to tyramine, differing only in that it possesses one more carbon atom on the aliphatic chain. It closely resembles benzedrine except that it possesses a hydroxy group in the para position in the benzene ring. These slight changes impart to the compound distinct actions which have therapeutic application.

Pharmacological Actions. Paredrine may be classified as a sympathomimetic amine. It is more stable than epinephrine and practically devoid of actions on the central nervous system. It promises to be of definite value as a mydriatic, is useful as a vasopressor agent when effects on the central nervous system are not desired, but seemingly its actions on the bronchi and gastro-intestinal tract are not sufficiently pronounced to be useful clinically.

Cardiovascular System. Paredrine has a pronounced pressor action. This is evident from experiments both on animals and human beings. Alles (1933) observed that after intravenous injection in anesthetized dogs, the compound was approximately $\frac{1}{50}$ to $\frac{1}{100}$ as active as epinephrine, but had a much more sustained pressor effect. In man, paredrine raises the blood pressure after oral, subcutaneous or intravenous administration, equipressor doses by these three different routes being approximately 20 to 40 mgm, 10 to 20 mgm, and five to 10 mgm, respectively (Abbott and Henry, 1937; Loman, Rinkel and Myerson, 1939). After oral or subcutaneous administration the pressor effect lasts from 90 to 120 minutes. The duration of the response to intravenous injection is about 20 to 30 minutes. Both the systolic and diastolic pressures are elevated, the former sometimes as much as 75 or 100 mm of mercury after the doses cited.

The rise in blood pressure apparently results from both myocardial stimulation and peripheral vasoconstriction. In isolated heart-lung preparations, paredrine accelerates the heart rate, decreases the systolic, diastolic and stroke volumes and increases cardiac output (Crismon and Tainter, 1938). In man, the drug produces modifications of the ventricular complex of the electrocardiogram characteristic of those seen after epinephrine, prevents or abolishes cardiac standstill produced by pressure on the carotid sinus, increases the rhythmicity of the ventricle in heart block (Nathanson, 1939), and supports the blood pressure during spinal anesthesia (Iglauer and Altschule, 1940). Although at the height of the pressor response from paredrine the heart rate is usually slowed, this is due to compensatory circulatory reflexes, and the administration of moderate doses of atropine abolishes the bradycardia (Iglauer and Altschule, 1940). Although many investigators have failed to notice cardiac irregularities resulting from paredrine, Abbott and Henry (1937) reported occasional instances of extrasystoles and persistent coupling.

Paredrine presents some interesting anomalies in its actions on blood vessels. The drug does not cause vasoconstriction when injected intradermally nor does it prolong the duration of action of local anesthetics. After systemic administration of the compound, skin temperature does not fall and indeed the patient may appear flushed. Nevertheless, it seems that vasoconstriction plays a prominent rôle in the pressor action of the drug, possibly the vessels of the splanchnic area responding more markedly than those of the surface. However, in accounting for the pressor effects of paredrinol and paredrine, Stead and Kunkel (1939) believe that the drugs may act on the venous side of the circulatory tree and that this may account largely for the pressor effect (*see* page 452). When the drug is applied to the normal nasal mucous membrane, blanching occurs from exposure to a 0.25 per cent solution and a strength of 1.0 per cent is adequate to shrink congested mucosae (Abbott and Henry, 1937).

Respiratory Tract. Alles (1933) reported that paredrine is effective in dilating bronchi whose musculature exhibited natural or induced tone. However, the drug is clinically ineffective in relieving attacks of bronchial asthma which readily respond to epinephrine (Abbott and Henry, 1937).

Eye. Paredrine, from the reports thus far available, is the most effective of the sympathomimetic amines in regard to mydriatic action and probably more closely approaches the ideal mydriatic than does any other compound. A one per cent solution produces complete dilatation of the pupil within 45 minutes and the effect lasts two hours. A three per cent solution produces complete dilatation within 30 minutes, the effect lasting approximately three hours (Powell and Hyde, 1938; Mayer, 1939). There is little action on accommodation and no significant change in intra-ocular tension. A combination of atropine or homatropine with paredrine causes both mydriasis and cycloplegia. The administration of one drop of a one per cent atropine solution or four per cent homatropine solution followed in three minutes by one drop of a one per cent paredrine solution results within 60 minutes in maximum mydriasis and cycloplegia. Following the homatropine-paredrine combination, effects begin to subside within four to five hours; newsprint can be read within eight hours; and the patient can resume normal use of the eyes within 18 hours. With the atropine-paredrine combination, normal function is restored after three days, but this is in contrast to the 10 to 14 days required when atropine alone is used to produce a comparable loss of accommodation. There is said to be no increase in intra-ocular tension associated with the use of paredrine combined with belladonna alkaloids (Tassman, 1938).

Central Nervous System. Paredrine apparently causes no stimulation of the central nervous system. In a comparative study of the central actions of a group of sympathomimetic compounds, Jacobsen (1938) concluded that only those drugs possessing a three carbon atom aliphatic chain linked to a benzene ring were central stimulants. With the introduction of hydroxy groups into the benzene ring, the property of central excitation was lost. This would account for the marked analeptic effects of benzedrine and the absence of this action in paredrine. All reports on the clinical use of paredrine note the absence of central stimulation.

Untoward Reactions. Paredrine causes few untoward reactions. In a series of 574 injections, Abbott and Henry (1937) record only three instances of toxic responses, these occurring after unusually large doses. The patients complained of intense headache, nausea and vomiting. The effects subsided within a few hours.

Absorption, Fate and Excretion. Paredrine is absorbed in an active form from the gastro-intestinal tract and parenteral sites of administration. The respective durations of activity for different routes of administration have been discussed. Seemingly the drug causes little local vasoconstriction. Thus, after subcutaneous injection paredrine gains rapid access to the circulation and causes a marked pressor response. Presumably the drug is inactivated by the tissues but specific information on its fate and excretion is lacking.

Preparations. Paredrine is not an official drug nor is it described in N.N.R. It is marketed as an ophthalmic solution containing one per cent paredrine hydrobromide and two per cent boric acid in distilled water. Paredrine salts may also be obtained in powder form for systemic administration.

Therapeutic Uses. Paredrine has received a fairly extensive trial in *ophthalmology*. It is a useful mydriatic when employed alone, and in combination with small amounts of atropine or homatropine it is valuable for the production of cycloplegia of brief duration. The drug is administered as outlined above and has the distinct advantages that it produces no irritation or increase in intra-ocular tension and that its effects, although maximal, are brief in duration. Altschule and Gilman (1939) reported on the use of paredrine hydrobromide in supporting the blood pressure during *spinal anesthesia*. Good pressor effects were obtained with 10 or 20 mgm intramuscularly, five or 10 mgm intravenously, or both. No untoward reactions were observed. Nathanson (1939) reported on the use of the drug in *Adams-Stokes disease* and cites one instance in which the patient was relieved of syncopal attacks for two months by the oral administration of paredrine hydrobromide in a dose of 60 mgm three times daily. Paredrine will probably receive more extensive clinical trial because its sustained action and lack of central effects make it a desirable agent in the treatment of certain circulatory disturbances.

PAREDRINOL

Paredrinol is a sympathomimetic amine which differs chemically from paredrine only in that it possesses a methyl group on the amino nitrogen. Its structure is presented in Table 21. Paredrinol was introduced in Germany in 1937 under the trade-name "veritol" and since then has been rather extensively investigated and used clinically in that country. The drug is available in the United States for experimental purposes, but has not been generally marketed.

Pharmacological Actions. The pharmacological actions of paredrinol are essentially similar to those of paredrine. The drug is a relatively stable vasopressor agent which is active after oral or parenteral administration. It has little or no stimulating action on the central nervous system, does not affect metabolic functions, and possesses no outstanding pharmacological properties except those manifested on the circulation. It is probably slightly less potent than paredrine.

Although the mechanisms of action of paredrine and paredrinol are probably the same, attention has been directed to the effects of paredrinol on the venous circulation. This is because Rein (1937), who first investigated the actions of the compound in experimental animals, noted that it produced a marked rise in venous pressure before the arterial pressure was affected. Rein failed to observe a decrease of the blood flow in the extremities and therefore attributed the pressor action to an intense discharge of blood from the splanchnic venous reservoirs. On the other hand, Heymans and Bayless (1937) present a much more orthodox viewpoint as to the mechanism of the pressor action, and on the basis of animal experiments conclude that the drug causes slight peripheral vasoconstriction and pronounced splanchnic vasoconstriction. Reis (1940) also supports the view that arteriolar rather than venous constriction is the basic mechanism of the pressor action.

Stead and Kunkel (1939) investigated the mechanism of arterial hypertension produced by paredrinol in normal human subjects. The drug caused a rise in both arterial and venous pressure but no change occurred in the blood flow of the foot, forearm or calf. Furthermore, intracutaneous injection of the drug did not cause localized vasoconstriction. However, Stead and Kunkel reasoned that increased peripheral resistance did occur for in spite of the greatly increased arterial pressure, blood flow through the tissues and cardiac output remained unchanged. They postulated two possible mechanisms of action: (1) primary constriction of certain portions of the minute vessels which regulate peripheral resistance, and (2) primary constriction of veins and emptying of the vascular reservoirs, causing an increased venous return to the heart and a redistribution of the blood in the arterial and venous portions of the circulation. In support of the latter mechanism of action they observed that if sodium nitrite is administered to individuals whose blood pressure was elevated by paredrinol, the pressure fell to normal only when the subject was in the upright position in which instance the combined actions of sodium nitrite and the upright position result in venous pooling of blood (page 556). When the subject reassumed a horizontal position, the blood pressure again rose to hypertensive levels. Stead and Kunkel reasoned that if the primary pressor effect of paredrinol is due to its actions on the venous circulation, which temporarily would result in an increased venous return and cardiac output, one could account for the peripheral vasoconstriction as that which would occur reflexly in regulating blood flow to a rate commensurate with metabolic demands.

In a more extensive study on the antagonistic actions of paredrinol and nitrites, Stead, Kunkel and Weiss (1939) observed that in many individuals paredrinol prevented the syncope which can be induced by the administration of sodium nitrite to patients in the upright position (page 556). They believe that paredrinol would be a useful drug in the treatment of circulatory collapse caused by the pooling of blood in a dilated venous system, but caution against its use in shock resulting primarily from a loss of fluid from the blood stream (page 586).

The fact that paredrine as well as paredrinol causes venous constriction and an increase in venous pressure in man is confirmed by Iglauer and Altschule (1940). These investigators attribute venous constriction to local stimulation by the drug but they do not believe that venous constriction is a factor in the production of arterial hypertension.

Therapeutic Uses. Paredrinol has been employed for the treatment of a variety of circulatory disturbances but has not received extensive clinical trial in the United States.

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CHAPTER 25

AUTONOMIC BLOCKING AGENTS

I. DRUGS INHIBITING STRUCTURES INNERVATED BY POSTGANGLIONIC CHOLINERGIC NERVES

ATROPINE, SCOPOLAMINE AND RELATED SYNTHETIC DRUGS

Historical. The drugs which inhibit structures innervated by postganglionic cholinergic nerves comprise the alkaloids of the belladonna plants. The two most important of these alkaloids are *atropine* and *scopolamine.*

Galenical preparations of belladonna have been employed in medicine for many centuries and were known to the ancient Hindus. The professional poisoners of the Middle Ages often employed the deadly nightshade plant to produce a type of intoxication which was often prolonged and obscure. This prompted Linné to name this shrub *Atropa belladonna,* after Atropos, the oldest of the Three Fates who severs the thread of life. The word "belladonna" itself is a reminder of the antiquity of these medicines in that it signifies "beautiful lady," the women of long ago being wont to instill a decoction of belladonna in their eyes to produce dilated pupils, a sign of comeliness. The resulting disturbance of vision evidently was a small price to pay for beauty. The mydriatic action of belladonna, so widely used today, was thus well understood hundreds of years before the invention of the retinoscope.

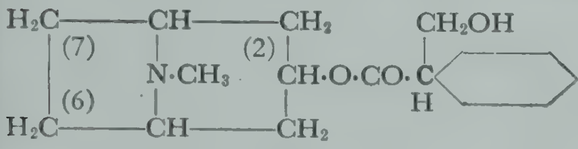
Accurate study of the actions of the belladonna drugs dates from the isolation of the pure alkaloids. Atropine was isolated by Mein in 1831 but it was not until the early part of the present century that pure samples of scopolamine became available. The inhibition by atropine of the cardiac effects of vagal stimulation was demonstrated by Bezold and Bloebaum (1867) and the prevention of salivary stimulation upon excitation of the chorda tympani was shown by Heidenhain five years later. These pioneer and fundamental observations were quickly followed by numerous others and today there exists as secure a body of experimental and clinical information on the actions of the belladonna alkaloids as is available for any other drug group.

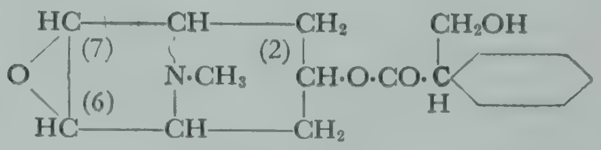
Sources and Members. The belladonna drugs are widely distributed in nature, especially in the Solanaceae plants. *Atropa belladonna,* the Deadly Nightshade, yields mainly the alkaloids *atropine* and *hyoscyamine.* The same is true of *Datura stramonium,* known as Jamestown or Jimson weed, stink weed, thornapple and devil's apple. The alkaloid *scopolamine* (hyoscine) is found chiefly in the shrub *Hyoscyamus niger* (Henbane) and *Scopola carniolica.* The galenical tincture and extract of belladonna, official in the U.S.P., are potent chiefly by virtue of their atropine content.

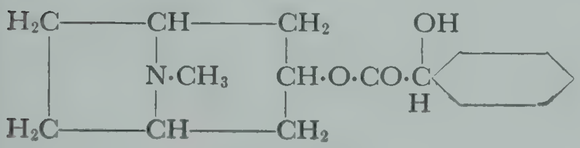
Chemistry. The synthetic chemist has not greatly improved upon the products of nature in this field, and although a few related derivatives have been introduced into medicine, they do not possess the wide range of therapeutic usefulness which characterizes the naturally occurring belladonna alkaloids. The natural belladonna alkaloids are organic esters formed by the combination of an aromatic acid, *tropic acid,* and complex organic bases, either *tropine* or *scopine.* The synthetic alkaloids usually contain mandelic instead of tropic acid, and a simpler organic base than tropine. The structural formulas of atropine and scopolamine and their relation to the synthetic drugs in the belladonna group appear in Table 24.

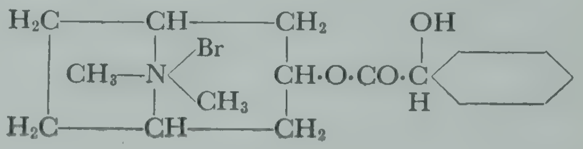
TABLE 24

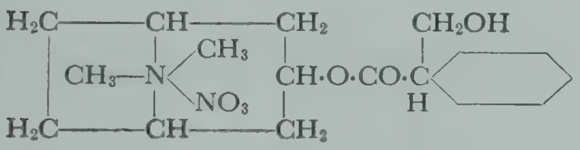
ALKALOIDS OF THE BELLADONNA GROUP AND ALLIED SYNTHETIC SUBSTANCES

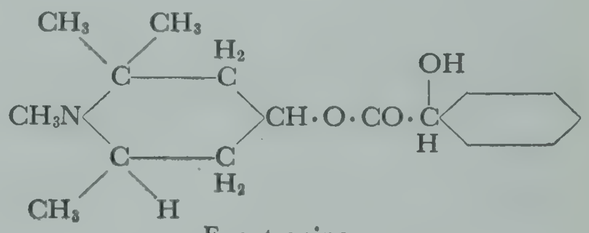

Atropine

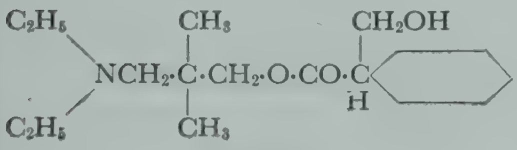

Scopolamine

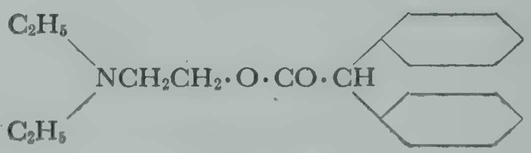

Homatropine


Novatropine


Eumydrine


Eucatropine


Syntropan


Trasentin

Scopine differs from tropine only in having an oxygen bridge between the carbon atoms designated as 6 and 7 in the above formulas. This alteration in structure is therefore the sole chemical distinction between atropine and scopolamine. *Homatropine* is a synthetic alkaloid produced by a combination of the base tropine with a somewhat simpler organic acid than tropic acid, namely, mandelic acid. *Novatropine* is merely the methylbromide of homatropine. *Eucatropine* (euphthalmine) is another synthetic alkaloid which is a combination of mandelic acid and a piperidine base. *Syntropan* is also a synthetic drug which is an ester of tropic acid and a tertiary amino alcohol, 3 diethylamino-2, 2-dimethyl-1-propanol. *Trasentin* contains neither tropic acid nor tropine, but merely retains the ester structure and the tertiary amino base.

The chemical relationship between these various natural and synthetic drugs, and their status, occurrence and optical activity, can readily be seen by reference to Table 25.

Relation of Chemical Structure to Pharmacological Action. Numerous chemical and experimental data indicate that the basis of the selective action of atropine on autonomic structures resides not in the tropine base, which is relatively inactive, but in the tropic acid radical. The esterification of tropic acid with a tertiary amino alcohol is the essential combination. The existence of a free hydroxyl group in the acid portion of the ester is

TABLE 25

ALKALOIDS OF THE BELLADONNA GROUP AND ALLIED SYNTHETIC SUBSTANCES

ALKALOID	STATUS	OCCURRENCE	BASE	ACID	OPTICAL ACTIVITY
Atropine	U.S.P.,B.P.	Natural	Tropine	Tropic	Racemic
Hyoscyamine		Natural	Tropine	Tropic	d and l forms
Scopolamine (l-hyoscine)	U.S.P.,B.P.	Natural	Scopine	Tropic	Levorotatory
*Atroscine (dl hyoscine)		Natural	Scopine	Tropic	Racemic
Homatropine	U.S.P.,B.P.	Synthetic	Tropine	Mandelic	Racemic
Eumydrine	Non-official	Synthetic	N-methyl nitrate of tropine	Tropic	Racemic
Eucatropine (euphthalmine)	N.N.R.	Synthetic	Piperidine derivative	Mandelic	Racemic
Novatropine	N.N.R.	Synthetic	Tropine N-methyl bromide	Mandelic	Racemic
Syntropan	N.N.R.	Synthetic	Tertiary amino propyl alcohol	Tropic	Racemic
Trasentin	Non-official	Synthetic	Diethylamino-ethylalcohol	Diphenyl-acetic acid	Racemic

* Not used clinically.

also important. Other aromatic acids may be substituted for tropic acid but the activity of the resulting compound is qualitatively altered. It is possible, however, to synthesize esters having parasympatholytic activity which contain neither tropic acid, scopine or tropine.

The presence of an asymmetric carbon atom in tropic acid (bold-faced C in the formula) allows for optical activity and stereoisomerism in this group of alkaloids. Scopolamine is levorotatory hyoscine and is much more active than *d*-hyoscine. Atropine is racemic, being a mixture of equal parts of the optical isomers of hyoscyamine. Inasmuch as dextrohyoscyamine has weak peripheral actions in the body, atropine owes its potency chiefly to its content of levohyoscyamine. The latter has the same central actions as atropine but is twice as powerful in its peripheral autonomic effects. The differences in behavior of atropine, dextrohyoscyamine and levohyoscyamine have been correlated with their relative rates of destruction in the body as well as with their specificity for autonomic effector organs. It is thought that levohyoscyamine exists in the younger portions of belladonna leaves and changes to racemic atropine as the plant grows older. The same change also occurs in galenical mixtures.

The close chemical relationship between atropine and cocaine deserves passing mention. *Ecgonine,* the organic base of cocaine, differs from tropine only in having a $COOCH_3$ attached at the carbon atom marked 2 in the formula for atropine. The acid portion of the cocaine ester is benzoic instead of tropic acid, and thus atropine and cocaine are tertiary amino esters of aromatic acids. Atropine, however, has only mild local anesthetic actions, and dulls rather than paralyzes sensory nerve endings. Cocaine in turn, has little or no parasympatholytic action. There are some tertiary amino esters of organic acids, however, which can act both as local anesthetics and parasympathetic depressants. The local use of belladonna in ointments, plasters and suppositories for relief of pain, though formerly rather extensive, is almost obsolete.

Mechanism of Action of the Belladonna Alkaloids. The major belladonna alkaloids, atropine and scopolamine, have two principal actions in the body. The first is on the central nervous system and the mechansim underlying these central effects is unknown. The second and more important action is on *smooth muscle* and *secretory glands* innervated by postganglionic cholinergic nerves. This latter action comprises the so-called "parasympathetic depressant" property of the belladonna drugs. All the muscarinic effects of acetylcholine and its esters can be prevented by atropine and many of the responses to cholinergic nerve stimulation can be blocked. The site of this action is directly on effector cells and not on nerve endings. The release of the chemical mediator is not prevented by atropine. Of purely academic interest is the fact that atropine under certain experimental conditions appears to exert some blocking effect on autonomic ganglia (Marazzi, 1939). This action, however, plays no part in the clinical use of the belladonna alkaloids and does not seriously challenge the previously developed concept that atropine blocks the muscarinic and not the nicotinic effects of acetylcholine. For the finer mechanism of atropine behavior, the reader is referred especially to page 340. The differences in the pharmacological properties of atropine, scopolamine and other alkaloids of this group will be mentioned as occasion arises in the following discussion.

Pharmacological Actions

Central Nervous System. Atropine produces stimulation of the medulla and higher cerebral centers. In usual clinical doses (0.5 to 1.0 mgm), this effect is manifested only by some central vagal excitation and moderate respiratory stimulation. The latter effect may be due to a direct action of atropine on the respiratory center. The rate and occasionally the depth of breathing are increased. When respiration is seriously depressed, atropine cannot be depended upon to produce excitation. Indeed, under such a circumstance, large or continued doses of atropine may cause even further depression of breathing. After doses bordering on the toxic, the central excitation produced by atropine becomes more prominent. Restlessness, irritability, disorientation, hallucinations and delirium may be evident. These effects are discussed under atropine poisoning. Ultimately, stimulation is followed by depression, and medullary paralysis is the cause of death from atropine. That all parts of the brain are not stimulated by atropine is seen in the "sedative action" exerted by belladonna alkaloids on the rigidity and tremor of parkinsonism. This action, which at present is viewed as central in origin, cannot be harmonized with an excitatory property of atropine. The drug, therefore, appears to have a primary depressant effect on certain central motor mechanisms, at least in parkinsonism. Homatropine and novatropine manifest little or no action on the central nervous system when administered in therapeutic doses.

Scopolamine, in its central actions, is usually said to contrast rather sharply with atropine. Whereas atropine first stimulates and then depresses the brain, scopolamine is a primary depressant and therapeutic doses normally cause drowsiness, fatigue and dreamless sleep. The sedative and tranquillizing effects of scopolamine have been described under preanesthetic medication. Not infrequently, however, therapeutic amounts of scopolamine produce excitement, restlessness, hallucinations and delirium. Some but certainly not all of these paradoxical reactions may be classed as idiosyncrasy or as due to the administration of scopolamine to individuals with pain. As was pointed out previously, non-analgesic sedatives given in the presence of pain are likely to cause excitement and delirium. When therapeutic doses of scopolamine are combined with morphine, as in preanesthetic medication, the pain threshold-raising property of morphine is not enhanced (Wolff and coworkers, 1940).

Scopolamine is often viewed as a respiratory depressant, but this action on the medullary respiratory center has been exaggerated. Indeed, strong evidence from clinical experiments of Waters and his associates (1938) indicates that the depression of breathing by morphine can be completely counteracted by balanced doses of scopolamine, so that otherwise poisonous amounts of morphine may be administered to man without lowering the normal respiratory exchange (page 48).

Peripheral Actions. By keeping firmly in mind the functional results of the paralysis of cholinergic nerves to smooth muscles and glands, one can accurately predict in most instances the pharmacological actions of the belladonna alkaloids. These drugs prevent the responses of smooth muscle and gland cells to cholinergic impulses. In a broad sense, the end-result often simulates overactivity of the sympatho-adrenal system—that is, it resembles the response to an injection of epinephrine. This is true because, after atropine, the normal adrenergic impulses remain dominant and unopposed.

Atropine and scopolamine differ quantitatively in their peripheral actions. Scopolamine is the stronger blocking agent for the iris, ciliary body, and certain secretory (salivary, bronchial and sweat) glands. The action of atropine is more pronounced and more prolonged than that of scopolamine on the heart, intestine and bronchiolar muscle. Atropine is more useful for its peripheral autonomic action than is scopolamine because in clinical doses it lacks a central sedative effect. Scopolamine is employed occasionally on the eye, but otherwise it is administered mainly for its central effects.

Eye. Atropine and scopolamine paralyze the sphincter muscle of the iris and the ciliary muscle of the lens to cholinergic nerve impulses and to acetylcholine. They thus cause dilatation of the pupil, *mydriasis,* and paralysis of accommodation, *cycloplegia.* The pupil is widely dilated and photophobia is present. The lens is fixed for far vision, near objects are blurred, and sometimes micropia is observed. When the drugs have exerted their full effects, the iris is no longer responsive to light and fails to react to convergence of the eyes—that is, the normal reflexes to light and accommodation are interrupted. These ocular responses are obtainable after local or systemic administration of the alkaloids. That the site of action is purely peripheral, however, is easily demonstrated by carefully applying a solution of atropine to only one-half of the cornea, whereupon dilatation of that half of the pupil alone occurs. The belladonna mydriatics differ from the sympathomimetic mydriatics (ephedrine, cocaine) in that the latter cause dilatation of the pupil without loss of accommodation. Pilocarpine and physostigmine are capable of constricting the atropinized pupil. The paralysis caused by atropine is thus not absolute. A fact of interest in comparative pharmacology is that atropine does not dilate the pupils of birds because their irides are composed of striated muscle and are paralyzed not by the belladonna alkaloids but by curare.

The intraocular pressure in normal eyes is not greatly disturbed by atropine or scopolamine. Mydriatics in general (except cocaine), however, tend to elevate this pressure especially when it is already above normal. This is true particularly of atropine due to its long duration of action. The mechanism of the rise in intraocular tension is disputed but the probable cause is the interference with the lymphatic drainage at the crucial angle of the eye due to the crowding back into this angle of the iris curtain.

Respiratory Tract. The belladonna alkaloids inhibit glandular secretions of the nose, pharynx and bronchi, and thus cause drying of the mucous membranes of the respiratory tract. This is especially prominent if there has been excessive secretion. The smooth muscles of the bronchi and bronchioles are relaxed, particularly by atropine, and this results in a slight widening of the airway and slight increase in the volume of residual air. It has been suggested that this increase in "dead space" due to bronchiolar dilatation may be the basis of the respiratory stimulation noted after atropine, but the evidence for this is not convincing. Atropine is considerably less effective than epinephrine as a bronchial antispasmodic, even when the degree of bronchoconstriction produced by faradic stimulation of the vagus nerve is used as an index of their antispasmodic potency (Figure 41).

Heart. The main effect of atropine on the heart is to alter *cardiac rate.* Atropine has a biphasic action on the heart rate. When average clinical doses are employed (0.5 to 1.0 mgm) the rate may temporarily be slowed due to a slight stimulant action of the alkaloid on the medullary vagal nuclei. This slowing is rarely marked or significant, and the change in rate is unaccompanied by changes in blood pressure, because of efficient cardiovascular compensatory mechanisms. After larger doses, usually not under 2.0 mgm in man, atropine causes an acceleration of heart rate due to the blocking of vagal effects on the S-A pacemaker. The increase in cardiac rate may be quite prominent in cases of atropine poisoning. The cardiac action of atropine is most noticeable in healthy young adults in whom the influence of the vagus on the cardiac pacemaker is at its height. At the extremes of life, in infancy and in old age, large doses of atropine may fail entirely to quicken the heart rate.

Adequate doses of atropine not only remove the heart from normal vagal control, but also prevent typical cardiac arrest from electrical stimulation of the vagus—"vagus arrest." The bradycardia or asystole produceable by injection of acetylcholine or its congeners is likewise prevented or abruptly halted by atropine. Cardiac slowing caused by other drugs, such as physostigmine, pilocarpine or muscarine, is also counteracted. Many types of *reflex* cardiac slowing mediated through the vagus nerves are prevented by adequate amounts of atropine, such as those due to inhalation of irritant vapors, to stimulation of the carotid sinus or to central stimulation of the vagal nuclei. The removal by atropine of vagal influence on the specialized tissue of the heart may also cause changes in conduction. In certain cases of partial heart block in which there is a vagal component as an etiological factor, atropine may lessen the degree of block. In some patients with complete heart block, the idioventricular rate may be accelerated by atropine. On the other hand, toxic doses of atropine may in themselves cause A-V block.

Circulation. Atropine in clinical doses counteracts completely the peripheral vasodilatation and sharp fall in blood pressure caused by acetylcholine and mecholyl. Yet when given alone, it does not have a striking or constant effect on blood vessels or blood pressure. Late in the course of atropine poisoning, the blood pressure may fall markedly, but this is due to central vasomotor depression. Toxic amounts of atropine usually, and therapeutic doses occasionally, cause an active vasodilatation of cutaneous blood vessels, especially of those in the blush area *(atropine flush).* The mechanism of this anomalous vascular response is unknown. It has been suggested that the flush is a compensatory action for the purpose of radiating heat to offset the atropine-induced rise in temperature. On the other hand, the reaction may be peripheral in origin and a direct vascular effect of the drug (Hamet, 1936). The scarlet appearance of the flushed skin, coupled with the rise in temperature which may accompany atropine intoxication, has caused the mistaken diagnosis of scarlet fever.

Although the vagal innervation of the coronary arteries is believed by some authorities to be vasoconstrictor in function, atropine is ineffective clinically in conditions of coronary vascular insufficiency and in angina pectoris. Nevertheless, atropine has been shown experimentally by competent workers to increase coronary blood flow. For example, Essex and associates (1940), employing the thermostromuhr technic in trained unanesthetized dogs, demonstrated that atropine markedly augmented coronary blood flow. An increased cardiac rate was an invariable accompaniment of the enhanced coronary blood flow, with the doses of atropine used (one to two mgm).

Gastro-intestinal Tract. The belladonna alkaloids affect both the secretory and motor activities of the gastro-intestinal tract. The *salivary secretions* are inhibited and this antisialogogic action causes the mouth to become dry, and swallowing and talking difficult. The statements that atropine lessens *gastric secretion* and lowers the acidity of the gastric juice need considerable correction. Such effects are noted only when large doses are given to experimental animals and the results cannot be interpreted to indicate that the belladonna drugs are clinically useful to diminish gastric secretion in peptic ulcer. The formation of hydrochloric acid is presumably rather under hormonal and chemical than under vagal control, and therefore one cannot expect to obtain significant changes by atropinization.

In *man,* the effect of atropine on the character of gastric secretion depends on a number of factors including the amount of drug administered, the phase of digestion and the presence or absence of disease. On the whole, the normal gastric secretion is not significantly altered by the belladonna drugs. The psychic phase of secretion, mediated by the vagus, is reduced but not abolished. The chemical phase of gastric secretion is not greatly altered by atropine. Volume may be slightly reduced, but acidity is not lowered. It is possible that the intestinal phase is somewhat inhibited, but this requires confirmation. Atropine likewise tends to diminish the continuous interdigestive secretion of the stomach. Furthermore, the duration of the effects of atropine on gastric secretion is brief when compared with that on the salivary glands.

The gastric cells responsible for the elaboration of mucin and enzymes are more directly under the influence of the vagi than are the acid-secreting cells, and full doses of atropine may decrease the concentration of these organic constituents. The secretion of an abundant gastric juice rich in both acid and proteolytic enzyme obtainable after the injection of the choline esters (mecholyl and doryl) or pilocarpine is blocked completely by atropine. Histamine-induced secretion is not impressively altered, although large doses of atropine may decrease the volume of the response. These facts offer little basis for the clinical use of the belladonna drugs in peptic ulcer or hyperchlorhydria in an attempt to reduce the volume and acidity of gastric juice.

The action of atropine on the secretion of the *intestinal glands, pancreatic juice* and *bile* is not significant and finds no therapeutic application.

The belladonna alkaloids exert definite effects on the *motility of the gastro-intestinal tract.* For an appreciation of these actions, it is necessary to recall certain facts concerning the influence of the extrinsic autonomic nerves on the movements of the enteric tract.

In general, cholinergic (parasympathetic) nerve impulses to the bowel enhance both tone and motility, but relax sphincters. The combination of these two factors favors the passage of chyme along the intestinal tract. In contrast, adrenergic (sympathetic) nerve impulses diminish the tone and motor activity of the enteric tract and contract sphincters, delaying the advance of the chyme (Table 17). Extrinsic nerve impulses alone, however, do not determine the activity of the bowel. The gastro-intestinal tract possesses a complex intrinsic neuromuscular mechanism whereby its motility is regulated, and impulses from the central nervous system serve only to allow a more delicate regulatory control. In addition, the antagonism between the two divisions of the autonomic nervous system is not as highly organized in regard to the bowel as it is, for example, in the case of the iris muscle of the eye. The depression of one system does not necessarily result in dominance of the other. This is particularly true of the sphincters of the intestine where the balanced opposition between the influences of the cholinergic and adrenergic nerves may break down entirely. It is known, for example, that stimulation either of the vagus or the splanchnic nerve to the stomach will cause increased tone when that organ is hypotonic, and decrease tone when it is hypertonic. The same principle appears true for the colon and for the sphincters of the alimentary canal. Thus epinephrine, which has little effect on the normal pyloric sphincter, enhances the tone when the sphincter is relaxed and diminishes tone when it is contracted.

The actions of autonomic drugs on gastro-intestinal motility are thus conditioned by the level of functional activity of the bowel at the time of administration of the drug. This principle holds true particularly for the belladonna alkaloids. In general, tone and peristalsis are decreased and sphincter activity is enhanced by atropine. The effects are much more prominent when spasm or hypermotility is present.

Although it is commonly stated that ordinary therapeutic doses of belladonna alkaloids have no significant influence on normal peristalsis, intubation studies combined with flouroscopy in normal human subjects indicate that clinical doses of atropine sulfate and tincture of belladonna produce definite and prolonged effects on the motor activity of the duodenum, jejunum, ileum and colon, consisting of a marked decrease in tone and in peristaltic movements, and of a less striking effect on rhythmical contractions (Elsom and Drossner, 1939). These results agree, in general, with those obtained with atropine on the human colon by Jackman and Bargen (1938).

Atropine does not significantly affect the gastric evacuation time in normal subjects. When the stomach is excessively motile and hypertonic, the alkaloid abolishes hyperactivity and restores normal peristaltic rhythm. For example, the augmentation of gastric contractions produced in man by morphine can be inhibited by atropine (Veach, 1937) (Figure 17), and the same is true for the hypermotility of the human stomach induced by injections of insulin (Quigley, 1937).

Atropine abolishes or prevents the *excess* motor activity of the gastro-intestinal tract induced by choline esters, pilocarpine, physostigmine and related parasympathomimetic drugs. For example, if an isolated strip of intestine is treated with pilocarpine to cause increased tone and spasm, the addition of atropine to the bath fluid results in immediate resumption of normal tone and peristalsis. The belladonna drugs are not effective in blocking the responses to such direct muscular stimulants as histamine and barium. Certain synthetic alkaloids appear to have more selective actions on the intestinal musculature than atropine. Although atropine blocks completely the effect of acetylcholine on the bowel, it is relatively ineffective in preventing the responses to stimulation of the vagus nerve. The physiological significance of this fact as well as a possible anatomical explanation have been discussed (page 340).

Other Smooth Muscle. On the *ureter,* the belladonna alkaloids exert an antispasmodic effect, especially noted when the ureter is in spasm. In man, atropine completely eliminates the increased ureteral tone caused by morphine (Figure 20), and the drug may also affect the normal activity of ureteral muscle. When the ureter is showing active contractions, atropine has an antispasmodic action (Figure 44).

On the *biliary ducts and gall bladder,* atropine exerts a mild antispasmodic action. This is not sufficient, however, to prevent or abolish the marked spasm and increased intrabiliary pressure induced in human beings by morphine. Both the nitrites and xanthines are more effective than atropine in this regard.

On the *uterus,* atropine has actions which are of little consequence, despite the fact that the drug is sometimes incorporated in prescriptions for dysmenorrhea. The extrinsic nerves to the uterus are relatively unimportant in the regulation of motility, and the motor response of the organ to drugs and nerve impulses differs depending on manifold factors, particularly the species involved, the presence of pregnancy and its stage. For these reasons, no didactic statement regarding the influence of atropine can be given, although in general it tends to be mildly antispasmodic.

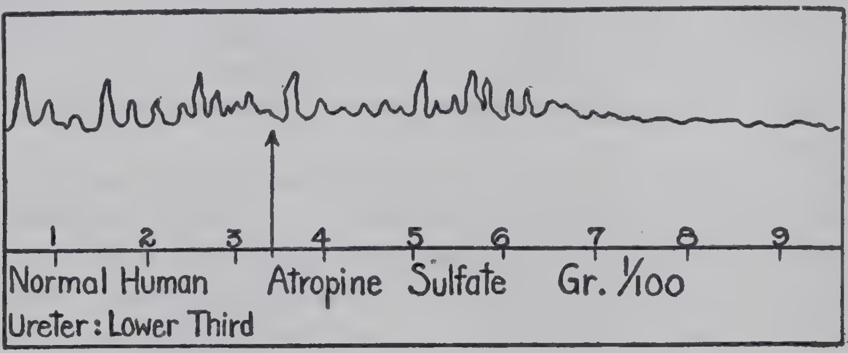


Figure 44. *The effect of atropine sulfate on the normal human ureter.*

Kymographic tracings obtained by means of ureteral catheter and water tambour; time in minutes. Note that within three minutes after the subcutaneous administration of 0.6 mgm of atropine sulfate the amplitude of contractions and ureteral tone are depressed. (After Ockerblad, Carlson and Simon, 1935. Courtesy of the *Journal of Urology.*)

On the *urinary bladder,* atropine exerts a depressant effect on the detrusor muscle, especially in conditions of hypertonus. This is the basis for its use in enuresis.

Sweat Glands. Atropine is a potent inhibitor of the sweat glands despite the vasodilatation it may cause in certain cutaneous areas. Sweating is suppressed and the skin becomes hot and dry. The prevention of insensible perspiration may be sufficient to elevate the body temperature, although hyperthermia is not prominent unless toxic amounts of belladonna have been taken. The anhidrotic action of atropine remained a pharmacological anomaly for many years due to the fact that sweat glands lacked parasympathetic innervation. The stimulation of sweating by pilocarpine likewise remained unexplained. With the demonstration that the nerves to sweat glands are cholinergic in function, the response of these structures to parasympathomimetic agents at once became clear.

Body Temperature. The increase in body temperature following the administration of belladonna alkaloids is significant only when large doses are given. Hyperthermia from moderate doses, nevertheless, may occur in children and infants and the term "atropine fever" has arisen to describe this phenomenon (White, 1929). Suppression of sweating is the main factor in the production of fever, although restlessness produced by toxic doses may contribute. It has also been suggested that atropine may cause fever by a central effect on temperature regulation. In atropine poisoning in infants, the temperature may reach the alarming height of 109 F. Animals which do not sweat, such as the dog, show no fever after atropine.

Local Analgesic Effects. The local anesthetic action of atropine has been mentioned under the discussion of the chemistry of the drug. The use of belladonna alkaloids for their anodyne property is practically obsolete.

Miscellaneous Actions. In man, atropine in ordinary doses does not significantly alter the *basal metabolic rate* or respiratory quotient. Edsall and Means (1914), however, noted in a study of two patients that atropine in doses of 1.2 mgm caused a definite rise in metabolism, a marked fall in alveolar carbon dioxide and a rise in alveolar ventilation. Despite the many contradictory experimental reports on the effect of atropine on carbohydrate metabolism, the level of *blood sugar* is not altered by clinical doses. Belladonna drugs do not affect the *secretion of milk*. Stockman (1927), however, has reported that atropine decreases the yield of milk when given to women post partum in doses of 0.6 mgm twice daily. This observation requires confirmation. *Lacrimation* is depressed due to inhibition of the tear glands, but this action of atropine is not as prominent as on the salivary glands. *Leukocytosis* may occur from atropine medication in children. *Voluntary muscles* of mammals are not directly affected by belladonna.

Tolerance. Tolerance to the belladonna drugs occurs in man to a limited extent. This is noticed particularly in patients with parkinsonism who eventually receive daily doses of atropine or scopolamine which, if given to the uninitiated, would result in poisoning. *Habituation* and *addiction* do not occur, although vomiting, malaise, perspiration and salivation have been recorded in patients with Parkinson's disease upon sudden withdrawal of the large doses required for therapeutic benefit.

Some species of animals, especially rodents and marsupials, are tolerant to large doses of belladonna alkaloids. Rabbits, for example, thrive on a diet containing belladonna leaves and do not manifest toxic effects. It appears that the serum and liver of tolerant animals possess the ability rapidly to destroy these alkaloids.

Absorption, Fate and Excretion. The belladonna alkaloids are absorbed rapidly from the gastro-intestinal tract. They also enter the circulation when applied locally to the mucosal surfaces of the body. Absorption occurs from the eye, and to some extent from the intact skin. Mydriasis and partial paralysis of accommodation lasting several days have occurred from the use of belladonna plasters. Atropine disappears rapidly from the blood and is distributed throughout the entire body. In the tissues, especially in the liver, the alkaloid is destroyed in large measure by hydrolysis of the ester to tropine and tropic acid. The remainder, amounting in man to about one-third the ingested dose, is excreted mainly within 14 hours by the kidneys. Traces are found in other secretions including the milk. Atropine readily crosses the placental barrier and enters the fetal circulation. The appearance of the alkaloids of belladonna in the urine allows for their recognition by a rapid and sensitive presumptive test. A single drop of urine placed in a cat's eye will dilate the pupil if atropine (0.0003 mgm) or scopolamine (0.00002 mgm) is present.

Poisoning by Belladonna Alkaloids. Atropine and scopolamine are the most important drugs of the belladonna group from the standpoint of poisoning. Intoxication frequently occurs in the clinical use of these agents. Children are especially susceptible and many cases of poisoning have resulted from the conjunctival instillation of these alkaloids, because absorption occurs from the nasal mucosa after the drug has entered the nasolacrimal duct or from the intestinal tract if it is swallowed. Serious poisoning has occurred from the erroneous substitution of scopolamine or atropine for the weaker homatropine. If the patient who is using belladonna in ascending doses for spastic states of the bowel is not warned concerning early signs of intoxication, unpleasant consequences may follow. The atropine in medicines given for enuresis in children has caused poisoning. Finally, berries or seeds containing belladonna alkaloids are occasionally ingested by children in toxic amounts, or a brew made from the seeds of Jimson weed may cause poisoning.

Hughes and Clark (1939), in an article reporting two instances of stramonium poisoning from the drinking of tea made from Jimson weed seeds, cite the following cases which occurred in 1676 and are probably the first to have been reported in the United States: "This being an early Plant, was gather'd very young for a boil'd salad, by some of the Soldiers sent thither, to pacifie the troubles of Bacon; and some of them ate plentifully of it, the effect of which was a very pleasant Comedy; for they turned natural Fools upon it for several Days. One would blow a Feather in the Air; another would dart straws at it with much Fury; and another stark naked was sitting up in a Corner, like a Monkey grinning and making Mows at them; a Fourth would fondly kiss and paw his Companions, and snear in their Faces, with a Countenance more antik than any in a Dutch Droll. In this frantik Condition they were confined, lest they in their Folly should destroy themselves; though it was observed that all their Actions were full of Innocence and Good Nature. Indeed, they were not very cleanly; for they would have wallow'd in their own Excrements, if they had not been prevented. A Thousand such simple Tricks they play'd and after Eleven Days, return'd themselves again, not remembering anything that had pass'd."

Fatalities from atropine and scopolamine are rare despite the therapeutic potency of low doses of these drugs, although Morton (1939) records two fatalities among eight cases of atropine poisoning in children. Of all the potent alkaloids, atropine has one of the widest margins of safety. Scopolamine is usually stated to be more toxic than atropine, although the evidence for this belief requires reexamination. Idiosyncrasy, nevertheless, is more commonly manifested toward scopolamine than atropine, and ordinary therapeutic doses may sometimes cause alarming intoxication. Mild toxic effects not infrequently noted after scopolamine have been attributed to chemical decomposition, but it appears that even the purest samples of the drug may show some variations in clinical action and toxicity.

The amounts of atropine required to cause definite symptoms of overdosage can be seen from the following table:

0.5 mgm	Slight cardiac slowing; some dryness of mouth.
1.0 mgm	Definite dryness of mouth and thirst; slowing of heart rate followed by some acceleration; mild dilatation of pupil.
2.0 mgm	Rapid heart rate; palpitation; xerostomia; inhibition of sweating; pupils dilated; some blurring of near vision.
5.0 mgm	All of above symptoms marked; speech disturbed; difficulty in swallowing; restlessness combined with fatigue; headache; dry and hot skin.
10.0 mgm and above	Above symptoms more marked; pulse rapid and weak; iris practically obliterated; vision very blurred; skin flushed, hot, dry, and scarlet hue; ataxia; excitement; restlessness; hallucinations, delirium and coma.

The *fatal dose* of atropine is not known but it is probably in the neighborhood of 100 mgm for adults and 10 mgm for young children. Survival has been reported after much larger doses and a case of recovery is on record after 500 mgm of scopolamine.

Symptoms. These develop promptly after ingestion of the drug. The mouth becomes dry and burns, and swallowing and talking are difficult or impossible. Marked thirst is present. The vision is blurred and photophobia is prominent. The skin is hot, dry and flushed. A rash may appear especially over the face, neck and upper part of the trunk, and desquamation may follow. The atropine rash is more likely to occur in children. The body temperature rises and in infants may reach the alarming height of 107 F or more. The pulse is weak and the cardiac rate is very rapid, although in infants and old people this acceleration may not be prominent. Palpitation is experienced and the blood pressure is elevated. Urinary urgency and difficulty in micturition are sometimes noted.

The patient is restless, excited and confused and exhibits weakness, giddiness and muscular incoordination. Gait and speech are disturbed. Nausea and vomiting are sometimes noted. The behavior and mental symptoms may suggest an acute psychosis. Memory is disturbed, orientation faulty, hallucinations (especially visual) common, sensorium clouded, and mania or delirium not infrequent. The diagnosis of acute schizophrenic episodes or alcoholic delirium has been mistakenly made, and some patients have been committed to psychopathic institutions. Atropine and scopolamine do not differ in these respects although depression follows the excitement and psychotic phenomena somewhat more readily after scopolamine.

The syndrome described persists for many hours and may completely disappear only after several days have passed. Depression and circulatory collapse result only in cases of severe intoxication. The blood pressure declines, respirations become inadequate and death due to respiratory failure occurs after a period of paralysis and coma.

Diagnosis. Careful analysis of the symptoms readily demonstrates that widespread paralysis of those structures innervated by postganglionic cholinergic nerves has occurred and this should immediately arouse the suspicion of belladonna poisoning. Particularly significant are the dry mucous membranes, widely dilated unresponsive pupils, tachycardia, cutaneous flush and fever. The last two features are prominent in children and should not be mistaken for an acute exanthematous illness such as scarlet fever. Atropine-induced leukocytosis may contribute to the possibility of such an error. The mental symptoms, however, may distract the physician's attention from the obvious peripheral autonomic signs. Any patient with an acute onset of bizarre mental and neurological symptoms should be suspected of drug poisoning, especially by atropine. History of belladonna medication is helpful in corroborating the diagnosis. If one is still in doubt, the hypodermic injection of 10 to 30 mgm of mecholyl (Dameshek and Feinsilver, 1937) may prove whether poisoning by atropine or scopolamine exists. If the flushing, salivation, sweating, lacrimation, intestinal hyperactivity, etc., characteristically seen after mecholyl do not occur, belladonna intoxication almost certainly is present, because atropine antagonizes all muscarinic effects of mecholyl.

Treatment. When the poison has been taken orally, gastric lavage with solutions containing alkaloidal antidotes may be undertaken. Potassium permanganate is ineffective in destroying atropine. Pilocarpine may be given in doses of five mgm and repeated at intervals until the mouth is moist. This adds to the patient's comfort and relieves the visual symptoms to some extent. Central effects of the poison, however, are not influenced by pilocarpine and represent the source of danger. If marked excitement is present, the short-acting barbiturates, chloral hydrate or paraldehyde may be used for their sedative action. Large doses should not be employed, unless essential, because of the danger that their central depressant action may coincide with the depression occurring in the late stage of belladonna poisoning. Central nervous system stimulants may be tried if the patient is observed after depression has developed. Artificial respiration or inhalation of carbon dioxide and oxygen may be necessary if respiratory depression is severe. Remaining therapy is purely symptomatic. Ice bags and alcohol sponges aid in reducing the fever in children. Careful nursing is essential.

Preparations, Doses and Routes of Administration. *Tincture of Belladonna,* U.S.P., B.P., is a widely employed preparation obtained from belladonna leaves. Its average dose is 0.6 cc which is the equivalent of approximately 0.2 mgm of atropine. *The Extract of Belladonna,* U.S.P., B.P., may be obtained in *pill* form or as a *powder* for capsules. Its dose is 0.015 gram.

Belladonna Leaf (Deadly Nightshade Leaf), *Belladonna Root* (Deadly Nightshade Root) and *Fluidextract of Belladonna Root* are also official in the U.S.P. and B.P. The average oral doses for adults of these three drugs are as follows: *Belladonna Leaf,* 0.06 gram; *Belladonna Root,* 0.045 gram; *Fluidextract of Belladonna Root,* 0.05 cc. These preparations, however, are little used, and preference is given to the tincture or extract of belladonna leaves and to the pure alkaloids. The U.S.P. and B.P. also contain a *plaster* and *ointment* form of belladonna, but these have few if any valid uses.

Atropine, U.S.P., B.P., the main alkaloid of belladonna, is available as such or as the readily soluble salt, *Atropine Sulfate,* U.S.P., B.P., in tablet or powder form. The usual adult dose is 0.3 to 1.0 mgm. The usual route of administration is oral, but solutions of atropine sulfate may be injected subcutaneously or intravenously. *Scopolamine* (hyoscine) is marketed as the readily soluble salt, *Scopolamine Hydrobromide* (Hyoscine Hydrobromide), U.S.P., B.P. The adult dose is 0.5 mgm. Scopolamine may be given orally or parenterally by injection.

The official stramonium preparations and their doses are as follows: *Stramonium* (U.S.P., B.P.), 0.075 gram; *Extract of Stramonium* (U.S.P.), 0.02 gram, available in pill and powder form; *Tincture of Stramonium* (U.S.P., B.P.), 0.75 cc.

The official preparations and doses of hyoscyamus (from *Hyoscyamus niger*) are as follows: *Hyoscyamus* (Henbane), U.S.P., B.P., 0.2 gram; *Extract of Hyoscyamus* (Extract of Henbane), U.S.P., B.P., 0.02 gram, available in pill and powder form; *Fluidextract of Hyoscyamus* (Fluidextract of Henbane), N.F., B.P., 0.2 cc; *Tincture of Hyoscyamus* (Tincture of Henbane), U.S.P., B.P., 2.0 cc. These drugs are rarely employed in modern therapeutics and are not recommended because of their uncertain actions.

The synthetic alkaloids related to the belladonna group are discussed at the end of this chapter. These drugs include *homatropine, eucatropine, eumydrine, novatropine, syntropan* and *trasentin.*

Therapeutic Uses

The belladonna alkaloids enjoy a broad range of therapeutic use in medicine and surgery. The clinical applications of these drugs are a direct outgrowth of the various pharmacological actions outlined in the preceding paragraphs, and may be discussed in parallel order. The ubiquitousness of the effects of belladonna, however, is also its major drawback because it is often impossible to confine the action of the drug to those structures at which therapy is directed. Thus, side-actions must be tolerated during belladonna medication in order to secure certain desired responses. For example, when the abolition of intestinal spasm is sought, coincident dry mouth and suppression of sweating must be viewed as entirely unrelated but unavoidable phenomena.

Clinical Uses of the Central Actions. Scopolamine is more widely employed than atropine for its central effects. Nevertheless atropine is occasionally injected as a *respiratory stimulant.* For this purpose, atropine sulfate may be given subcutaneously in a dose of 0.5 to 1.5 mgm, but should not be repeated. In cases of severe central depression, other drugs than atropine are to be preferred. Therapeutic doses of scopolamine do not influence respiration.

The *sedative* and *tranquillizing* properties of scopolamine are useful especially in patients who are restless and agitated, as in *delirium tremens, maniacal states, cardiac and hyperthyroid psychoses,* etc. Scopolamine has also been employed to obtain criminal confessions. The value of scopolamine combined with morphine for preanesthetic medication has been discussed elsewhere. The depression caused by this combination of drugs is known as "twilight sleep," formerly widely used in *obstetrical anesthesia.* Its dangers far outweigh its advantages. The administration of scopolamine in conjunction with barbiturates in obstetrics has received considerable attention. Only persons specially trained in obstetrical anesthesia should routinely employ these potent drug combinations. Scopolamine is also of value in the *withdrawal treatment* of narcotic or alcoholic addicts (page 216). The usual sedative dose of scopolamine is 0.5 mgm of the hydrobromide salt, given orally or subcutaneously. Mild paradoxical responses or idiosyncrasy are not infrequent. If pain is present, scopolamine hypnosis may cause delirium unless analgesics are concomitantly prescribed.

In *paralysis agitans and postencephalitic parkinsonism,* therapy with belladonna alkaloids is one of the few measures that offers some measure of symptomatic relief. Atropine was apparently first recommended by Charcot, and scopolamine was introduced for the same purpose by Erb in 1901. A majority of patients experience improvement after these drugs are given. Tremor, muscular rigidity, abnormal gait, speech and posture, oculogyric crises, dysphagia, hyperhidrosis and sialorrhea respond favorably, and consequently the mental outlook often improves. Treatment is purely palliative and the course of the disease is not altered. The preparations usually employed are atropine, scopolamine, and tincture or extract of stramonium. No fixed dosage can be recommended but the important point is that the amount used varies with each patient and must be sufficient to afford optimal benefit. Ordinarily, very large doses are required and are reached by starting with small amounts which are then gradually increased. One may have to approach the limit of tolerance before real relief appears and mild toxic symptoms of annoying dry mouth and slightly impaired vision may be experienced. The local application of eserine may be necessary to overcome the mydriasis. Ultimate doses as high as five mgm or more of scopolamine or atropine, and five cc of tincture of stramonium, three times daily, are not unusual. The highest recorded daily dose of atropine is 54 mgm; of scopolamine, 195 mgm (!) (Hall, 1937; Cohen and Craw, 1937). Considerable tolerance obviously develops because such large amounts would be highly toxic to the uninitiated. Patients on high doses may be very sensitive to hot weather. Glaucoma is a definite contraindication to the employment of these alkaloids. The combined use of benzedrine and atropine may give more relief than atropine alone, especially in regard to oculogyric crises (page 446).

"Bulgarian Treatment" of Parkinson's Disease. This treatment consists in the use of an extract of belladonna root rather than of the pure alkaloids or galenical preparations of the leaf. It is claimed that better results are obtained and that unpleasant side-actions are fewer. There is no good evidence that Bulgarian belladonna root is more satisfactory than roots grown elsewhere. While it is possible that the particular combination of alkaloids of belladonna found in the root of the plant may be more beneficial to some patients than the use of other preparations, considerably more evidence is necessary to establish this point.

Belladonna alkaloids, particularly scopolamine, have been tried in other spastic and rigid states (*progressive spastic paralysis, spastic paraplegias due to birth injuries,* etc.) and variable degrees of symptomatic relief may sometimes be obtained.

Clinical Uses of the Peripheral Actions. *Ophthalmological Applications.* When the effects of belladonna alkaloids on the eye are desired, local rather than systemic administration is selected. Mydriasis is often necessary for proper examination of the retina and optic disc, and is valuable in the therapy of acute iritis, iridocyclitis, and keratitis of both the ulcerative and interstitial type.

Alternated with miotics, the belladonna mydriatics are employed for breaking up or preventing adhesions between the lens and the iris. Complete cycloplegia may be necessary in iridocyclitis, choroiditis and for accurate measurement of refractive errors. The usual preparation of *atropine* employed in ophthalmological work is a one per cent aqueous solution of the sulfate salt, although the alkaloid may be used as the free base in a one per cent solution in oil, or as a one per cent ointment. One or two minims of the aqueous or oily solution are instilled in the conjunctival sac, and pressure exerted in the region of the inner canthus will prevent the drug from reaching the nasal mucosa, where it may be absorbed in amounts sufficient to cause untoward systemic effects. This maneuver is particularly advisable in children. Gelatin discs containing atropine are sometimes employed instead of the solution and are inserted in the conjunctival space.

Atropine is repeated at intervals of several hours depending upon the degree of paralysis desired. Mydriasis without paralysis of accommodation is obtainable with a smaller amount of the drug than that necessary for cycloplegia. The pupillary dilatation produced by a full single instillation of atropine in healthy eyes persists for days, often ten or more; the cycloplegia, for four or five days. During acute inflammation, however, medication may have to be repeated two or three times a day. If satisfactory results are not obtained with a one per cent solution, the strength may be raised cautiously to two per cent, or the atropine may be combined with cocaine, benzedrine or paredrine. Atropine occasionally may cause local irritation of the eyes and in susceptible persons it may produce swelling of the eyelids and conjunctivitis. Upon continued atropine medication, conjunctivitis may become chronic and resemble trachoma.

Scopolamine hydrobromide may be substituted for atropine, particularly if the latter causes local irritation. A 0.1 to 0.5 per cent solution is used, and systemic absorption should be prevented by pressure over the lacrimal sac for five minutes after each instillation. Mydriasis is somewhat shorter in duration and intraocular pressure is affected less markedly than is the case after atropine.

When mydriatics are prescribed, dark glasses should be worn by the patient to lessen photophobia. Physostigmine is often helpful in overcoming belladonna mydriasis and one minim of a 0.2 per cent solution is applied several times daily until the pupil has returned to normal. A one per cent solution of pilocarpine nitrate may be employed similarly.

The main danger in the ophthalmological use of the belladonna drugs is that of increased intraocular pressure. An attack of glaucoma may be precipitated by the improper selection of a mydriatic agent, and blindness may ensue. Great care must therefore be exercised in instilling atropine in the eyes when there is a suggestion of increased intraocular tension. The pressure should be tested beforehand. Atropine should not be given to patients over 40 years of age, as a general rule, unless this drug is specifically indicated. A summary of the uses and dangers of mydriatic and miotic alkaloids in ophthalmology has been given by Gifford (1939).

The temporal characteristics of the mydriatic effects of atropine and scopolamine in comparison with homatropine, eumydrine and euphthalmine are presented in Table 26.

Respiratory Tract Disorders. Bronchial Asthma. Theoretically, atropine should be very effective in this syndrome because it dilates and dries the bronchial tree, and should thus counteract the bronchial spasm and excess glandular secretion. The results of atropine medication in acute attacks, however, are far from brilliant. Although an occasional patient responds satisfactorily to large doses, the drug cannot be relied upon to give relief in severe cases. Rather one uses epi-

Table 26

MYDRIATICS OF THE BELLADONNA GROUP

Drug	Strength of Solution %	Mydriasis		Paralysis of Accommodation	
		Maximal (hours)	Recovery (days)	Maximal (hours)	Recovery (days)
Atropine Sulfate	0.5–1.0	½	5 to 12	2 to 4	4 to 5
Scopolamine Hydrobromide	0.1–0.2	½	3 to 5	1 to 3	2 to 4
Homatropine Hydrobromide	2.0	½	½ to 1½	1 to 2	1
Eumydrine	0.5	½	½ to 1	1	1 to 3
Euphthalmine	5 to 10	½	½	......	......

nephrine and other measures. The belladonna alkaloids are time-honored remedies in asthma, nevertheless, and are often incorporated in various mixtures given for chronic asthma, or during the free period between acute episodes to diminish the frequency or severity of attacks.

The burning of *stramonium leaves* for the relief of asthma was introduced from India in 1802 by General Gent. This old remedy is occasionally employed today and may be helpful to some patients when used early or in mild attacks. Stramonium (2 parts), potassium nitrate (1 part), and powdered anise (1 part) are mixed together and one teaspoonful ignited, the smoke being inhaled. Some of the alkaloids of the burning leaf as well as some nitrite are contained in the smoke, and these agents tend to relieve bronchiolar spasm. The smoke, however, is irritating to certain individuals and may occasionally increase susceptibility to asthmatic attacks. The odor is rather unpleasant and clings about the room for some time. Proprietary asthma powders and cigarettes usually contain stramonium.

Coryza and Hay Fever. In acute rhinitis, coryza and hay fever, atropine may be helpful through inhibiting the nasal and lacrimal glands and thus giving symptomatic relief from distressing excessive secretions. Proprietary "cold" tablets often contain atropine for this purpose. The course of the illness is not altered by the drug.

Miscellaneous Respiratory Uses. The *preanesthetic employment* of atropine or scopolamine to prevent excessive secretions of the respiratory tract during inhalation anesthesia has been mentioned. *Bronchorrhea* from other causes may yield symptomatically to these alkaloids. In patients too feeble or exhausted to raise obstructing mucus from the trachea or bronchi, atropine may have to be employed if suction is not feasible. *Cardiac asthma* does not respond to atropine because the pulmonary edema which characterizes this syndrome is not the result of glandular secretion but is due to vascular stasis secondary to left ventricular failure.

Cardiovascular Uses. Atropine is occasionally of some value in the treatment of *premature systoles.* The alkaloid is also serviceable in patients experiencing *bradycardia* or complete systolic arrest with *syncope* as a result of abnormally active *carotid sinus reflexes.* Weiss and associates (1936) have shown that therapeutic doses of atropine abolish the vagal type of syncope in patients with hyperactive carotid sinus mechanisms, but have no effect either upon the depressor or cerebral forms of attacks. *Abnormal slowing* of the heart due to such poisons as pilocarpine, physostigmine, choline esters and certain species of mushrooms can be counteracted by atropine in full doses (2.0 mgm).

In *complete heart block* with syncopal attacks (Stokes-Adams disease), atropine may sometimes give relief, but more often the drug fails to affect the idioventricular rhythm. This is probably due to the fact that the vagus nerves do not innervate the human ventricle and also have little or nothing to do with the etiology of the arrhythmia in the vast majority of cases. Some acceleration of the ventricular rate may be regularly demonstrated in patients with complete heart block if atropine is given intravenously in doses of two mgm (Gilchrist, 1933). The drug, however, is least helpful when it is most needed, because at low initial ventricular rates the response to atropine is not significant. There is a rare type of auriculoventricular dissociation, however, probably of reflex origin, in which relatively small doses of atropine (0.5 to 1.0 mgm) given two or three times daily may abolish the block.

The higher the initial resting rate, the greater is the ventricular acceleration obtained. It has been suggested that the inherent rhythmicity of the specialized tissue at the center of idioventricular impulse formation determines the degree of acceleration from atropine in complete heart block. When the lesion producing the arrhythmia is high in the conduction system, a greater response will occur after atropine than when the new center of impulse formation is at a lower level. Epinephrine, in contrast to atropine, has a much greater accelerating effect in complete heart block when the initial ventricular rate is slow. The change in *auricular rate* after atropine in complete heart block is variable. Acceleration usually occurs but is unrelated to initial rate or ventricular response.

Atropine is sometimes useful for the prevention of *nitritoid crises* occurring in the course of arsphenamine therapy for syphilis. A subcutaneous injection of one or two mgm of the alkaloid is given 20 minutes before the arsenical. Epinephrine, however, is more effective and less unpleasant for this purpose.

Gastro-intestinal Disorders. In the therapy of *peptic ulcer,* no decrease in acidity or volume of gastric juice can reasonably be expected from belladonna alkaloids. On the other hand, tincture or extract of belladonna and atropine sulfate are serviceable in this disorder to control excess motor activity such as hyperperistalsis, pylorospasm and reflex spasticity of the colon. The drugs, however, are merely adjuvants to the more important dietary and medical management of peptic ulcer. Belladonna is also helpful in treating spastic constipation arising from various causes. In *mucous colitis, dysenteries, nonspecific chronic ulcerative colitis,* etc., these alkaloids are useful to control spasm, reduce hyperirritability, relieve pain and decrease the frequency of bowel movements. In *biliary colic,* atropine may be employed but satisfactory relief of symptoms is not the rule. Intravenously injected atropine (one to three mgm), given once or twice daily for several days, has been reported to give relief in the *gastric crises* of tabes dorsalis (Alajouanine and Harowitz, 1932). This observation requires confirmation.

Pylorospasm and *cardiospasm* may also be lessened or abolished by atropine. The roentgenologist sometimes finds this alkaloid of service in gastro-intestinal *x-ray studies* when there is difficulty in distinguishing between functional spasm and defects due to organic disease. Atropine administration has been recommended as a differential *diagnostic test* in questionable cases of *appendicitis.* If pain and tenderness persist after a hypodermic injection of 0.6 mgm of atropine, the likelihood of appendicitis is increased. Miscellaneous syndromes in which belladonna is used include *lead colic, morphine-induced obstipation* and *functional constipation* resulting from long train or auto trips.

Certain features of belladonna medication for disorders of the gastro-intestinal tract deserve special mention. Full dosage and long-continued administration are usually necessary in chronic cases. The optimal amount must be found for each patient, and varies greatly in different individuals. Some persons obtain benefit only when the dose used is just short of that which causes toxic symptoms. The tincture of belladonna is a convenient preparation because its dose can readily be adjusted. The usual practice is to start with small quantities, about 0.3 to 0.6 cc (five to 10 minims) three times daily, one-half hour before meals. The amount is then elevated at the rate of 0.06 cc (one minim) per dose per day until optimal relief is afforded. This may necessitate from two to three cc (30 to

45 minims) two or three times daily. Dry mouth may appear before satisfactory effects on the bowel are obtained, but this does not constitute a reason for decreasing the dose. Medication may have to be continued until evidence of intoxication is manifest, especially early difficulty in vision, dizziness, palpitation and nausea. The dose is then lowered to a level just below that which causes these symptoms. Failure to prescribe amounts of belladonna sufficient to act satisfactorily on the bowel has caused much unnecessary disappointment in the use of this valuable drug. The patient must be forewarned concerning the symptoms produced by belladonna and when to stop his medication. Otherwise serious poisoning may develop.

Urinary Tract Disorders. The antispasmodic action of atropine on the ureter may occasionally be employed to give relief from *ureteral colic.* The alkaloid is particularly indicated if morphine is employed because it will counteract the additional spasm of the ureter caused by morphine. In disturbances of the urinary bladder, especially in *enuresis* in children, atropine may give symptomatic relief by inhibiting excess detrusor tone. The pressure in the bladder of the child is lowered and the frequency of contractions decreased. Belladonna has been employed in other disorders of vesical function but the results are not brilliant. Langworthy (1936) found it of value in relieving the *urgency and frequency* of urination in patients with spastic paraplegia. The mechanism of action of atropine on the urinary bladder and sphincters is not always clear, probably due to the complex neurogenic control of the voluntary and autonomic components of these structures.

Miscellaneous Uses of Atropine. Atropine is employed more or less empirically in *dysmenorrhea* due to uterine spasm, and in certain cases it may afford relief. For this purpose the drug is given orally in 0.5 mgm amounts three times daily for two days preceding the expected onset of menstrual flow, and is continued for two days after menstruation has started. The alkaloid is useful for suppression of *excessive salivation,* such as may occur in heavy metal poisoning. Although atropine is an effective *anhidrotic,* the suppression of sweating is rarely employed in modern therapeutics. The belladonna drugs are helpful within limits in overcoming some of the symptoms of *poisoning* by pilocarpine, eserine, choline esters, and certain species of *Amanita.* Atropine has been employed prior to *encephalography* in doses of 1.3 mgm to lessen the symptoms which follow the injection of air into the subarachnoid space, such as nausea, vomiting, headache and excessive sweating. Good results have been reported by Scott (1939) in over 100 cases.

SYNTHETIC SUBSTITUTES FOR BELLADONNA ALKALOIDS

Novatropine

This drug is homatropine methyl bromide, and represents the mandelic acid ester of tropine methyl bromide. It differs from homatropine only by having a CH_3 and a Br radical attached to the N of tropine (Table 24). Novatropine is said to be less active than atropine on the central nervous system. Like homatropine, it is a weaker and less toxic autonomic blocking agent than atropine. The drug is used mainly for gastro-intestinal disorders for which it can be employed in the same manner as atropine.

Novatropine, N.N.R., is a white, bitter, water-soluble powder and is marketed for oral use in tablets containing 2.5 mgm.

Syntropan

This synthetic alkaloid is the phosphate salt of the tropic acid ester of a tertiary amino alcohol (Table 24). Its close resemblance to the local anesthetics in chemical structure is obvious, and the amino-containing base is the same as that used in the local anesthetic, *larocaine*. Syntropan is practically devoid of mydriatic action, being only $1/1000$ as effective as atropine and shorter in duration of action. Inhibition of pilocarpine-induced salivation in rabbits is manifested by syntropan to only $1/100$ the extent of atropine. The blocking of vasodepressor effects in cats is only $1/500$ as prominent with syntropan as with atropine. In sharp contrast, the spasmolytic action of the drug on isolated rabbit intestine is about $1/100$ to $1/20$ that of atropine (*see* Fromherz, 1937; Clark and coworkers, 1939).

The main action of syntropan is an antispasmodic one on smooth muscle, especially of the gastro-intestinal tract. The drug has been used to relieve gastro-intestinal spasm, vesical and urethral spasm and dysmenorrhea. The relaxation of smooth muscle is perhaps accomplished rather by a direct effect on muscle, in a manner similar to that of papaverine and nitrites, than by a specific parasympatholytic property, as is the case with atropine. The use of syntropan allows more discrete therapeutic results and one can obtain relief of spasm without accompanying mydriasis, dry mouth, and changes in cardiac rate.

Syntropan, N.N.R., a white, crystalline, water-soluble powder, is marketed for oral administration in tablets containing 50 mgm, and for hypodermic injection in ampules containing 10 mgm of drug in one cc of solution. The single dose may be repeated three or four times daily.

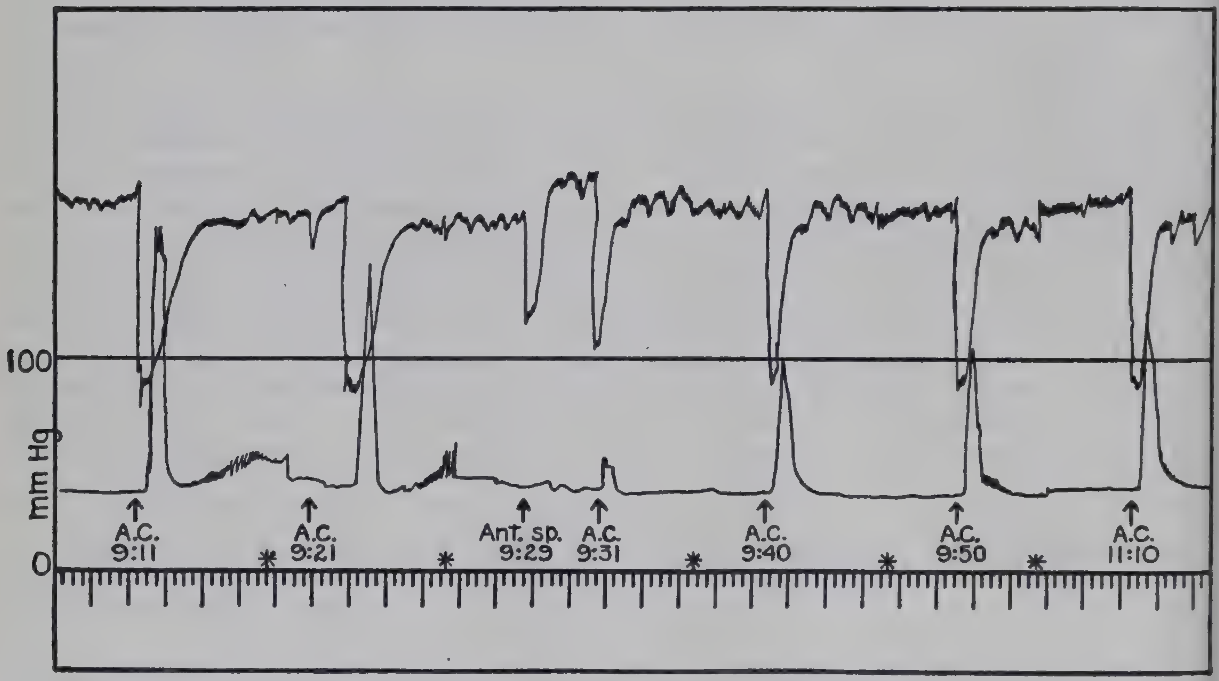


FIGURE 45. *The selective antispasmodic action of synthetic atropine substitutes.*

Anesthetized cat prepared for recording of carotid blood pressure and intestinal tone. Water manometer attached to balloon in jejunum under pressure of seven centimeters of water. Time in minutes. Control intravenous injection of acetylcholine (0.01 mgm/kg) causes a transitory increase in intestinal tone and fall in blood pressure. Two minutes after the intravenous injection of the antispasmodic (trasentin, 2.0 mgm/kg), the administration of acetylcholine is without effect on the bowel but still lowers the blood pressure almost as much as previously. Note how rapidly the antispasmodic action is lost when the drug is administered by vein. Observe that the rapid intravenous injection of the antispasmodic is accompanied by a transitory fall in blood pressure.

Synthetic atropine substitutes (see text) may be of value for their antispasmodic action when it is desired to avoid the cardiovascular, glandular and pupillary actions of the belladonna alkaloids. (Mountain, 1937.)

Trasentin

This synthetic alkaloid is another antispasmodic drug which has been recommended as a substitute for belladonna. Chemically, trasentin is the hydrochloride of the diethylamino ethyl ester of diphenylacetic acid. It thus contains neither the tropic acid nor tropine base of atropine, and has the type-structure of the local anesthetics (Table 24). Indeed, it has local anesthetic properties. One may wonder whether the anodyne action which is reported to occur from the use of trasentin in patients with peptic ulcer may not, in some measure, be due to a local anesthetic action of the drug. Trasentin accomplishes its antispasmodic effect on smooth muscle by a direct action in a manner similar to that of syntropan rather than through a highly selective parasympatholytic property, as is the case with atropine. Thus trasentin can counteract direct muscular stimulants like barium and pituitrin more effectively than does atropine, but it is much less potent against parasympathomimetic drugs such as the choline esters (*see* Johnson and Reynolds, 1937; Mountain, 1937; Necheles and coworkers, 1939). It lacks the mydriatic, cardiac and glandular effects of the belladonna alkaloids and thus, like syntropan, is more selective in its therapeutic action on smooth muscle (Figure 45). Trasentin apparently disappears rapidly from the body and has no cumulative action (Samaan and Saad, 1938).

Trasentin has been used especially for the same gastro-intestinal disorders in which atropine is indicated (Einhorn, 1938; Spier and associates, 1939). It has also been employed in spastic dysmenorrhea (Kurzrok and coworkers, 1940), and in spastic conditions of the gall bladder and biliary ducts, ureters, urinary bladder, and bronchi (Crassousi, 1937; Einhorn, 1938). The drug is marketed in oral tablets containing 75 mgm each, the dose being one or two tablets two or three times daily. Trasentin is also supplied in ampules containing 75 mgm in 1.5 cc of solution. The single hypodermic dose is 50 to 75 mgm. Trasentin is not official and is not included in N.N.R.

Homatropine

The chemical structure of this synthetic alkaloid has been given (Table 24). Homatropine may be viewed pharmacologically as a weakened atropine because it is both less active and less toxic than atropine. For example, from five to 10 times more homatropine than atropine is required to block the effects of vagal impulses. The drug is used solely for its actions on the eye and is employed as a one or two per cent solution of its hydrobromide or hydrochloride salt, or in the form of gelatin lamellae. Homatropine mydriasis is brief in duration. Homatropine is thus preferable to atropine when an extended increase in intraocular pressure must be avoided. Also, the patient is not inconvenienced by prolonged disturbance of vision due to cycloplegia. Homatropine is ineffective, as a rule, for the production of cycloplegia in children. The drug has been employed as a mydriatic in combination with ephedrine, paredrine and benzedrine. Repeated administration of homatropine to the eyes will result in satisfactory and fairly transient paralysis of accommodation. This requires the use of three or four drops of a two per cent solution every 10 or 15 minutes for one or two hours. The effects subside in approximately 24 hours.

Homatropine Hydrobromide, U.S.P., B.P., is the only official preparation. It consists of colorless crystals or a white, crystalline powder, soluble in six parts of water.

Eumydrine

Eumydrine is a methyl nitrate salt of atropine (atropine-N-methyl nitrate) (Table 24). It is occasionally employed in a solution of 0.5 per cent as a mydriatic, being less potent and less persistent in action than atropine. The peripheral autonomic effects of the drug are qualitatively similar to those of atropine but are less marked. At one time eumydrine was employed to suppress sweating. It has also been used in the treatment of pyloric stenosis in infants (Dobbs, 1939). The drug is not official and is not included in N.N.R.

Eucatropine

This synthetic drug was introduced as *euphthalmine.* Its chemistry has been mentioned (Table 24). It is employed solely as a mydriatic and causes no paralysis of accommodation. The action of eucatropine on the pupil is rapid and brief in duration. Maximal dilatation occurs in 30 minutes, and the iris returns to normal in two or three hours. The drug is thus safe and convenient to use and has no deleterious effect on intraocular pressure.

Eucatropine Hydrochloride, N.N.R., a white, odorless, water-soluble, granular powder, is administered as a five or 10 per cent solution, two or three drops being instilled into the eye, or tiny tablets of the alkaloid containing 1.5 mgm may be inserted directly in the conjunctival sac where solution in the tears is rapidly effected. The peripheral actions of eucatropine closely resemble but are weaker than those of atropine.

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CHAPTER 26

AUTONOMIC BLOCKING AGENTS

II. DRUGS INHIBITING STRUCTURES INNERVATED BY ADRENERGIC NERVES

ERGOTAMINE AND ERGOTOXINE

Drugs which inhibit effector cells from responding to adrenergic nerve impulses or to epinephrine belong in the main to two classes. The first group is composed of two natural alkaloids found in ergot—*ergotoxine* and *ergotamine*. The second group consists of synthetic *dioxane derivatives.* In addition, a number of miscellaneous drugs also block the responses of sympathetically innervated structures. These include *yohimbine,* its diastereoisomer *corynanthine,* and *apocodeine.*

The history, chemical nature and general pharmacology of the ergot alkaloids are discussed elsewhere (page 654), and it is necessary to consider here only those features which pertain to their autonomic properties. The dioxane derivatives are mainly of academic interest and have not been widely employed in therapeutics. *Yohimbine,* an alkaloid obtained from a West African tree (*Yohimbéhé*), likewise has no valid therapeutic uses although at one time it was employed in hypertension and promoted as an aphrodisiac. *Corynanthine* also remains chiefly an experimental drug.

Mechanism of Action of Sympathetic Blocking Agents. Drugs which inhibit the responses to adrenergic nerve stimulation or to epinephrine act peripherally on effector cells. The details of this action have been discussed (page 340) in relation to the concepts of humoral transmission of nerve impulses. Ergotoxine and ergotamine prevent effector cells from responding both to adrenergic nerve impulses and to epinephrine. Hence these drugs are both *sympathicolytic* and *adrenolytic.* The chemical mediator (adrenine or sympathin) is still liberated in the ergotoxinized animal but effector cells no longer respond to it. Ergotoxine and ergotamine differ little from each other and are effective in preventing augmentative rather than inhibitory sympathetic responses. Indeed, after the administration of these alkaloids, epinephrine or sympathetic nerve stimulation may no longer cause a rise in blood pressure and may even produce a fall. This reversal of response is referred to as *epinephrine-reversal* by ergotoxine (page 403; Figure 40).

The dioxane derivatives differ from ergotoxine and ergotamine. The best known of these compounds is 2-piperidinomethyl-1,4-benzodioxan, commonly called *Fourneau 933* or *933F.* This drug is *adrenolytic* and not sympathicolytic, that is, it blocks the response of effector organs to epinephrine but not to adrenergic nerve impulses. In this respect, 933F is analogous to atropine. Closely related dioxanes, however, differ from 933F in having more ability to annul the responses to nerve stimulation, as for example, *883F* (2-diethylamino-ethyl-1,4-benzodioxan). The ability of the dioxanes to block transmission in autonomic ganglia in a manner similar to nicotine is apparently unrelated to their peripheral sympathicolytic or adrenolytic action on effector cells. Yohimbine is chiefly adrenolytic. There is some *in vitro* evidence that 933F may owe part of its blocking action to an ability to facilitate the destruction of epinephrine (Morison and Lissak, 1938).

ERGOTAMINE AND ERGOTOXINE

Preparations. *Ergotoxine ethanesulfonate,* although an official reference standard in the U.S.P. and widely used experimentally, is not easily obtainable in the United States. The closely allied alkaloid *ergotamine,* on the other hand, is readily available as the *tartrate* salt (Gynergen, N.N.R.). This is marketed in tablets (one mgm) for oral or sublingual administration and in solution in ampules (one cc containing 0.25, 0.5 or 1.0 mgm) for intravenous or hypodermic injection. The details of the preparations of ergot alkaloids are given on page 661. Their chemical structure is discussed on page 655.

Inasmuch as *ergotamine tartrate* and *ergotoxine ethanesulfonate* have practically the same pharmacological properties, discussion may be limited to ergotamine because of its wider use and the greater body of clinical information which has accumulated concerning it.

Clinical Properties of Ergotamine. The pharmacology of ergotamine is presented under ergot. This drug shares with other ergot alkaloids the ability to stimulate the smooth muscle of the uterus and blood vessels. Ergotamine depresses the receptive mechanism of organs innervated by adrenergic nerves. In human beings, however, ergotamine in therapeutic doses (0.5 mgm subcutaneously) manifests only slightly and irregularly this autonomic blocking effect. For example, ergotamine reversal of the rise in blood pressure caused by epinephrine cannot be demonstrated in man. In fact, when epinephrine is injected following ergotamine, the blood pressure may rise more than with epinephrine alone, probably due to the direct vascular constriction caused by the ergot alkaloid. On the other hand, the elevated metabolic rate and increase in blood sugar induced in man by one milligram of epinephrine are partially inhibited by ergotamine. The typical inhibition seen experimentally in laboratory animals after large doses of ergotamine is not elicitable clinically.

Although ergotamine is employed for a miscellaneous group of clinical syndromes, the mechanism of action involved cannot be explained satisfactorily. Clinical uses of ergotamine are described here for convenience of presentation, and it must not be assumed that benefit is due to inhibition of sympathetic responses.

Therapeutic Uses

Migraine. Ergotamine tartrate is a valuable agent for relieving migrainous headaches, having been introduced by Maier in 1926 for this purpose. The drug slowly gained favor until today it is viewed by a number of clinical investigators as a fairly specific agent for symptomatic therapy of migraine.

Mechanism of Action. Ergotamine is not a sedative or analgesic, and other forms of pain are not influenced. Its specificity for migraine is indicated by the fact that only occasionally are other types of headache relieved. Indeed, ergotamine may cause headache in normal persons (Lennox, Storch and Solomon, 1936). It has been suggested that migraine is due to vasospasm and that ergotamine may act to relax the involved meningeal or cerebral blood vessels by blocking the effects of sympathetic nerve impulses. The vasospastic etiology of migraine, however, has not been proved (Storch, 1937), and it is doubtful whether therapeutic doses of ergotamine exert autonomic blocking effects in man. Furthermore, ergonovine, which lacks a sympatholytic action, is moderately effective in migraine.

Attempts have been made to correlate the direct vascular constriction produced by ergotamine with its efficacy in migraine. In both normal and migrainous individuals, the drug causes an increase in cerebrospinal fluid pressure and cerebral blood flow. These effects are probably secondary to the rise which occurs in the systemic blood pressure, for both the systolic and diastolic levels are elevated and the pulse pressure and pulse rate are decreased. Other agents, such as epinephrine or inhalation of carbon dioxide, which cause similar or greater responses in cerebral blood flow, however, do not uniformly relieve headache. Clinical investigations on this subject do not lend support to the theory that migraine is accompanied by generalized cerebrovascular spasm or abnormalities of intracranial pressure (Lennox, Gibbs and Gibbs, 1935; Pool, Storch and Lennox, 1936).

The effect of ergotamine on arterial tone is also reflected in the marked decrease in pulsation of the temporal arteries which occurs after therapeutic doses in patients with attacks of migraine (Graham and Wolff, 1938; Wolff, 1938). The pulsation of the temporal artery is reduced by 40 to 50 per cent coincident with the ergotamine-induced relief of migraine. A parallel decline has been noted in the amplitude of the arterial pulsation and the intensity of the headache (Figure 46). On the basis of these findings, it has been suggested that migraine may be associated with an increased amplitude of pulsations of cranial arteries.

Dosage and Route of Administration. Subcutaneous or *intramuscular* injection is the usual method of administering ergotamine tartrate. The dose is 0.25 to 0.5 mgm, and this may be repeated if the migraine is not relieved or if it recurs. No more than one mgm should be given in 24 hours. Occasionally ergotamine may be given *intravenously,* but this route should be employed only by those who are thoroughly familiar with the use of the drug. The intravenous dose is usually 0.25 mgm and must not be more than 0.5 mgm. The latter amount is the maximum allowable in 24 hours.

Tablets of ergotamine may be given *sublingually,* the dose being three or four mgm given as soon as the headache starts. One or two mgm may be given hourly thereafter, if necessary, until a total of 10 mgm has been taken. The average initial dose for *oral* ingestion is four to five mgm, and two mgm may be swallowed each hour thereafter until not more than 11 mgm have been taken.

The smallest amount effective in relieving the headache should be employed. Overdosage is the chief cause of untoward effects from ergotamine. The therapeutic courses outlined should not be repeated within the same week. After the drug has been given, the patient should lie down in a quiet, dark room for at least two hours. The speed and thoroughness of the relief from pain are directly proportional to the promptness with which medication is started after the onset of an attack. The preferred time to administer ergotamine is during the prodromal stage. By giving the drug early, the dose may be decreased considerably. If the seizure has reached its peak, larger amounts of ergotamine are needed. Not only does the drug then require a longer time for effective action, but unpleasant side-effects from medication are more pronounced. When more than eight mgm of ergotamine are required by the oral route in order to obtain relief or if the headache is severe, it is better to resort to the subcutaneous injection of 0.5 mgm. Oral medication is less effective than parenteral but may be satisfactory for mild or incipient attacks of migraine. The reason for the large oral dose is that ergotamine is poorly absorbed from the intestinal tract.

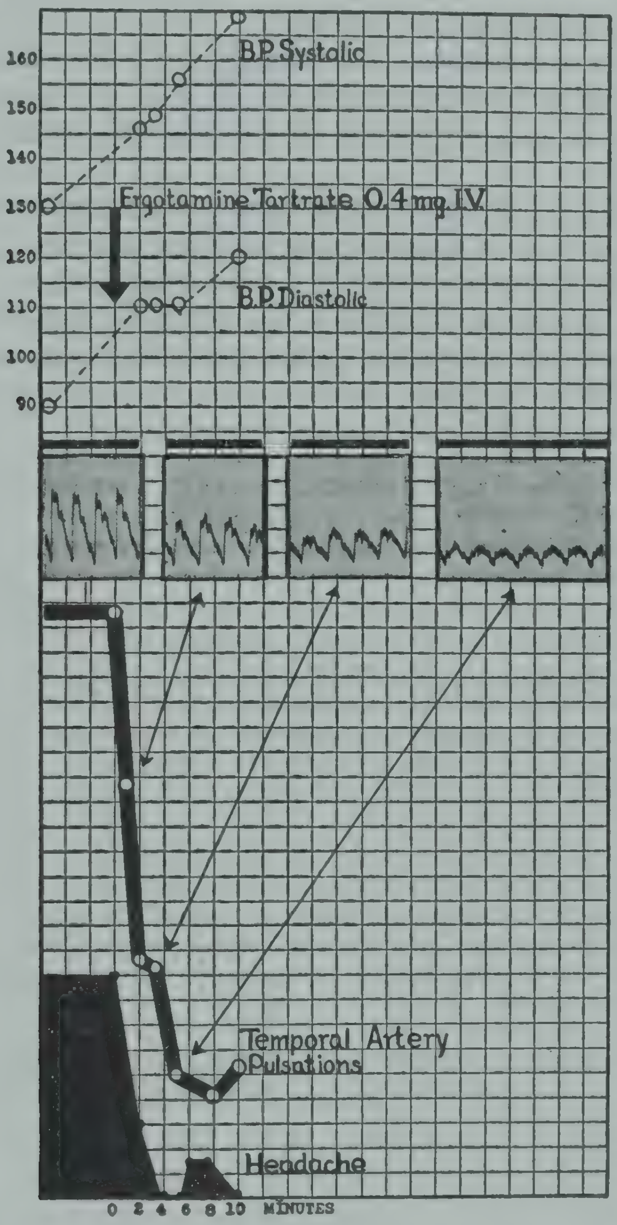

Figure 46. *Graphic representation of the response of migraine to ergotamine.*

The solid black line with open circles represents the average amplitude of pulsation of the temporal artery for any given minute before and after the intravenous administration of 0.4 mgm of ergotamine tartrate, the control amplitude being taken as 100%. Pulsation of the artery was measured by means of a tambour connected to a Frank capsule, the movements being photographically recorded. The individual pulsations are shown in the inserts of representative photographic records. The time line above the photographic records is in one-second intervals.

Note the rapid decline in intensity of headache (shown at bottom in solid black) after ergotamine, which is parallel both in time and degree with the decline in amplitude of pulsation of the temporal artery. The blood pressure rise seen here is not a constant feature of ergotamine therapy of migraine. Relief of headache is attributed to constriction of cranial vessels by the drug and consequent reduction in amplitude of their pulsations. (After Graham and Wolff, 1938. Courtesy of the *Archives of Neurology and Psychiatry.*)

Efficacy. The consensus of clinical opinion is that ergotamine is effective in the vast majority of cases (Lennox and Storch, 1935; O'Sullivan, 1936; Storch, 1938). Approximately 90 per cent of all patients or all attacks are relieved. The specificity of ergotamine for migraine is indicated by the fact that only 15 per cent of non-migrainous headaches are aborted. Relief is often dramatic. After parenteral injection of ergotamine, the headache may disappear in 15 minutes, but two hours or more may be required. Oral medication is much slower in bringing relief, averaging five hours, and it may fail in severe attacks. Continued use of the alkaloid does not result in diminished efficacy in subsequent attacks, provided adequate dosage is employed. The drug is not a cure and does not decrease the frequency of migraine headaches. Tolerance does not develop to ergotamine. The drug is not used to prevent attacks due to the danger of ergotism from continued medication.

Ergonovine in Migraine. Ergonovine, a newer alkaloid of ergot (page 658), is only moderately effective in migraine, terminating the headache in 37 per cent of 78 cases reported by Lennox (1938) and affording partial relief in 40 per cent. It has the advantages, however, that it is relatively more selective than ergotamine when given orally and that untoward gastro-intestinal symptoms are not so pronounced. Patients in whom ergonovine provides satisfactory surcease from attacks of migraine usually prefer this alkaloid to ergotamine.

Other Uses. The *obstetrical use* of ergotamine is given on page 667. The alkaloid has been tried in patients with *thyrotoxicosis* on the basis that many symptoms of the disease may be related to overactivity of the sympathetic nervous system. Clinical results have been disappointing, and furthermore a relatively large number of accidents from ergotamine have been reported in this group of patients. The drug has been used to relieve the generalized *itching* which occurs in jaundice, cirrhosis of the liver, leukemia, Hodgkin's disease, etc. The mechanism of the antipruritic action is unknown. The suggestion that the drug acts on sensory nerve endings seems improbable. Although relief is occasionally striking, ergotamine should be employed cautiously, if at all, for this purpose. Especially should it be avoided if the itching is due to hepatic disease.

Ergotamine has been suggested for the therapy of a variety of disorders without sufficient evidence for its efficacy or safety. These include certain psychoses, epilepsy, hypertension, paroxysmal tachycardia and tabetic cord-bladders. In none of these cases is the drug of value. The occasional success obtained with ergotamine in postural hypotension is probably related to the direct vascular (pressor) action of the alkaloid. The necessity for continued medication and the occurrence of unpleasant or toxic side-effects limit the usefulness of ergotamine in this syndrome. Ephedrine and related drugs are much safer and more serviceable.

Complications. A number of untoward effects may be noted from ergotamine therapy. These are especially likely to occur if large or frequent doses are employed or if the alkaloid is administered in the face of definite contraindications. Storch (1938) reviews 42 "accidents" reported in the literature. Twenty-three of the accidents occurred in obstetrical cases, and 11 in hyperthyroid patients. Gangrene occurred in 21 instances and there were eight deaths. Storch estimates that ill effects follow ergotamine in only 0.01 per cent of the cases in which the alkaloid is used. He calls attention to the fact that when ergotamine is prescribed in correct dosage in the absence of contraindications, it is a safe and useful drug and that no serious complications have been reported from its use in the migraine syndrome.

Ergotamine is capable of producing all the symptoms of ergotism. These are described elsewhere (page 660). Certain unpleasant effects, however, are seen with sufficient frequency during ergotamine therapy of migraine to deserve special mention here. Nausea and vomiting occur in a large number of patients, particularly after oral administration of ergotamine. Atropine sulfate (0.5 mgm subcutaneously) often relieves these gastro-intestinal effects. Weakness in the legs is common, and muscle pains in the extremities, which occasionally are quite severe, may occur. The intravenous injection of calcium gluconate (10 cc of a 10 per cent solution) may be used to relieve these pains, if they do not respond to massage and exercise. Numbness and tingling of the fingers and toes are other reminders of the ergotism which this alkaloid may cause. Precordial distress and pain suggestive of angina pectoris have also been noted, as well as transient attacks of tachycardia or bradycardia. Localized edema and itching may occur rarely in certain sensitive patients. Most of the effects enumerated are not alarming and do not require cessation of ergotamine therapy unless organic pathological conditions underlying the symptoms are demonstrable.

Contraindications. Sepsis is a definite contraindication to ergotamine therapy because pre-existing infection has been present in a number of cases in which ergotamine has caused gangrene. The drug should not be used in patients with vascular disease, such as syphilitic arteritis, marked arteriosclerosis, coronary artery disease, thrombophlebitis, and Raynaud's and Buerger's syndromes. Diseases of the liver or kidney are also contraindications. Serious accidents have been reported from the use of ergotamine in patients with pruritus (Comfort and Erickson, 1939; Yater and Cahill, 1936), especially when it is secondary to hepatic disease. Although it is difficult to cause abortion with ergotamine, pregnancy constitutes an objection to its use. Fortunately, migraine often ceases with the onset of pregnancy.

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CHAPTER 27

AUTONOMIC BLOCKING AGENTS

III. DRUGS INHIBITING AUTONOMIC GANGLIA AND SKELETAL MUSCLES

NICOTINE AND CURARE

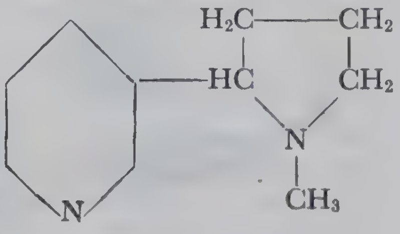
NICOTINE

Nicotine was discovered by Posselt and Reiman (1828) who isolated it from tobacco leaves. Orfila (1843) initiated the first pharmacological studies of the alkaloid and Langley and Dickinson (1889) described the actions of the drug on autonomic ganglia.

Using nicotine as a pharmacological tool, Langley (1889, *et seq.*) studied the sites of ganglionic synapse of autonomic efferent fibers, and in this manner greatly enlarged our knowledge of the physiology of the vegetative nervous system. He discovered that nicotinic paralysis of an autonomic ganglion prevents responses to preganglionic but not to postganglionic nerve stimulation. Therefore, if a fiber passes through a particular ganglion without synapsing, it is unaffected by application of nicotine to that ganglion. Conversely, if a nerve pathway is blocked by applying nicotine to a ganglion, it is presumptive evidence that a synapse occurs in that ganglion.

Although nicotine has no therapeutic uses, it is of great pharmacological interest. Furthermore, its high toxicity and presence in tobacco give nicotine a measure of medical importance. Preparations of nicotine are unofficial and available only for experimental purposes. The sulfate and salicylate salts as well as the liquid alkaloidal base are available.

Chemistry. Nicotine is one of the few liquid alkaloids. It is colorless, volatile, strongly alkaline in reaction, and on exposure to air it turns brown and acquires the odor of tobacco. The alkaloid is readily soluble in water and forms water-soluble salts. It is of interest to compare the structural formula of nicotine, which shows it to be a combination of a pyridine and a pyrollidine ring, with that of nicotinic acid and coramine.



Nicotine

Mechanism of Action. The autonomic action of nicotine consists of a primary transient stimulation and secondary more persistent depression of all sympathetic and parasympathetic ganglia. This is due to a direct action on ganglion cells, first to excite and then to paralyze them. During the stage of nicotinic stimulation, preganglionic impulses are more effective; during the stage of paralysis, preganglionic impulses are wholly ineffective. The effects of postganglionic stimulation, however, are quite unimpaired. Nicotine does not interfere with the release of acetylcholine in ganglia by impulses from the cholinergic preganglionic fibers, but renders the ganglion cells temporarily more sensitive and then more resistant to the chemical mediator. The effects of nicotine on skeletal muscle are similar to those on ganglia. In the stage of paralysis, nicotine thus manifests a curare-like action which is largely the basis for the toxic effect of the alkaloid on respiration. The relationship between synapses in autonomic ganglia and the junctions between motor nerve endings and skeletal muscles has been referred to (page 342) and provides a basis for understanding the curare-like action of nicotine. Curare, however, is much more specific for skeletal muscles than for ganglia, and the reverse is true for nicotine.

The expression "nicotinic action," which is applied to the action of choline esters on autonomic ganglia and skeletal muscles, arises from the similarity between the stimulatory effects of nicotine and acetylcholine on these structures (page 339).

In addition to its peripheral actions, nicotine affects the central nervous system. Here, again, the drug first stimulates and then paralyzes nerve cells.

Pharmacological Properties. The complex and often unpredictable changes which occur in the body after administration of nicotine are due not only to the several sites of action indicated above, but also to the fact that the alkaloid has stimulant and depressant phases of action. The ultimate response of any one structure may thus represent the algebraic summation of the different effects of nicotine. How complex these actions are may be understood by considering that the drug can speed the heart rate by the excitation of sympathetic or paralysis of parasympathetic cardiac ganglia, but can cause bradycardia by paralysis of sympathetic or stimulation of parasympathetic cardiac ganglia. In addition, the effects of the drug on the medullary centers influence the heart rate, as do also the vascular reflexes resulting from changes in the blood vessels caused by nicotine. Finally, nicotine tends to produce a discharge of epinephrine from the adrenal medulla and this hormone accelerates the cardiac rate and raises the blood pressure.

Central Nervous System. Nicotine markedly stimulates the central nervous system. This is particularly evident for the respiratory, vasomotor and emetic centers of the medulla. Motor stimulation manifests itself in convulsions. The excitation of *respiration* is a particularly prominent action of nicotine and has been investigated especially by Heymans and associates (1931) and by Wright (1935). Although large doses of the drug stimulate breathing by a direct action on the medulla, smaller amounts appear to act reflexly on respiration through the excitation of the chemoreceptors of the carotid body.

Stimulation of the central nervous system is followed by depression, and death results from failure of the respiration. It appears, however, that before the medullary centers are completely paralyzed, the peripheral curariform effect of nicotine on skeletal muscle may incapacitate the muscles of respiration.

Peripheral Nervous System and Skeletal Muscles. The autonomic ganglionic actions of nicotine and its curare-like effect on skeletal muscles have been described. Nicotine blocks impulse conduction through nerve trunks only when applied directly to the nerve in high concentration.

Circulation. The effects of nicotine on the circulation are complex, as explained above, due to the multiple sites of action of the alkaloid. The *rate* of the heart is usually slowed at first, due especially to stimulation of the central vagal nuclei and cardiac vagal ganglia. Tachycardia is prominent later, or with larger doses, due to vagal ganglionic paralysis coinciding with stimulation of cardiac sympathetic ganglia. Various types of *arrhythmia* have been reported experimentally from large doses, and are due either to accentuated vagal or sympathetic nerve impulses or to a direct action of nicotine on the heart muscle. The *blood pressure* is elevated due to peripheral vasoconstriction resulting from central vasomotor and sympathetic ganglionic stimulation. In late stages of poisoning, the blood pressure falls due to vasomotor paralysis. The smaller *vessels* of the periphery, especially those of the skin, are constricted after nicotine, but may dilate when the sympathetic ganglionic stimulation passes into the stage of paralysis. The coronary vessels are said to share in the primary vasoconstriction.

Gastro-intestinal Tract. The nauseant effect of nicotine is well known to every one who remembers smoking his first cigar. Vomiting may also occur. These effects are mainly central in origin. Increased motor activity of the bowel, occasionally leading to diarrhea, may result from parasympathetic ganglionic stimulation. This can be blocked by atropine and is followed by a stage of inhibition of intestinal tone and motility.

Glandular Effects. Nicotine causes a primary stimulation of salivary and bronchial secretions which is followed by inhibition. The salivation caused by smoking is reflexly produced by the irritation of the smoke rather than by the nicotine because the subcutaneous injection of 0.4 mgm of the alkaloid (the amount that may be absorbed by smoking two cigarettes of common blend) does not stimulate saliva in smokers or nonsmokers (Schnedorf and Ivy, 1939). In dogs with gastric pouches, nicotine (0.2 to 1.0 mgm) given subcutaneously either has no effect on or causes a decrease of the acid production of the fasting stomach and the gastric response to a standard test meal (Schnedorf and Ivy, 1939). The secretion of milk in lactating women who smoke moderately is evidently not disturbed. The adrenal medulla is stimulated and then depressed by nicotine so that an increased output of epinephrine may accompany the stimulatory phase of action on sympathetic ganglia. The similarity between the adrenal medulla and autonomic ganglia in their responses to drugs has been discussed (page 332).

Absorption, Fate and Excretion. Nicotine is readily absorbed from the oral and gastro-intestinal mucosa and from the respiratory tract. Sufficient absorption may also occur from the skin to produce severe poisoning. Nicotine is detoxified to a large extent in the body, especially by the liver, and the remainder is excreted, mainly in the urine. Nicotine can be isolated in the form of its salts in the urine of tobacco smokers. Excretion is evidently slower than was formerly believed and three to four days are required after an individual has stopped smoking before most of the drug disappears from the urine. Nicotine appears to be the substance responsible for the marked pressor action of many specimens of urine, and the factor of smoking must be eliminated in studies on hypertension when human urines are examined for a "pressor principle" (Helmer, Kohlstaedt and Page, 1939).

Acute Nicotine Poisoning. Nicotine is one of the most toxic of all drugs and acts with a rapidity comparable to that of cyanide. Poisoning may occur from accidental ingestion of insecticide sprays in which nicotine is present as the effective agent. The lay use of tobacco infusions as enemas against intestinal parasites has resulted in death. Tobacco contains large amounts of the alkaloid and it is said that the nicotine content of one cigar approximates two lethal doses for man. The fatal dose for man is probably in the neighborhood of 60 mgm, although four mgm or less usually produce alarming symptoms in non-habituated individuals.

The onset of symptoms of severe, acute nicotine poisoning is rapid, and death may occur within a few minutes. Due to its alkalinity, the drug has a local caustic action in the mouth and stomach. Nausea and salivation quickly appear and are followed by abdominal pain, vomiting and severe diarrhea. Headache, dizziness, disturbed hearing and vision, mental confusion and marked weakness are experienced. Respiration is stimulated and the blood pressure may be elevated. The pupils are constricted but later become dilated. The pulse is usually slow at first and rapid terminally. Faintness and prostration ensue, the blood pressure falls, breathing is difficult, the pulse is weak, rapid and irregular, and collapse may be followed by terminal convulsions. Death results from respiratory failure due to paralysis of the muscles of respiration.

Therapy. Occasionally death is delayed sufficiently to allow treatment to be instituted. Primary attention should be paid to the failure of the respiration. This has been shown to be peripheral in locus and due to the curariform effect of the alkaloid on skeletal muscles. Inasmuch as nicotine is destroyed in the body with fair rapidity, death may be averted if the patient can be tided over the interval necessary for detoxication of the poison. Artificial respiration should therefore be instituted and continued as long as necessary or until the heart ceases to beat. Central respiratory stimulants are not indicated as a rule. The amount of nicotine necessary to cause central medullary paralysis is greater than that needed for peripheral interference with respiration (Franke and Thomas, 1936). Other therapy is purely symptomatic.

Tolerance. Tolerance develops to nicotine if the drug is repeatedly administered. This is quite evident in confirmed tobacco smokers who are unaffected by amounts of the alkaloid (eight mgm) which would cause marked symptoms in the tyro (Wahl, 1919). Cross-tolerance exists between nicotine and the closely related alkaloid lobeline.

Tobacco and Chronic Nicotine Poisoning

Tobacco is the dried leaf of *Nicotiana tabacum,* a plant indigenous to America but now grown in many parts of the world. The early settlers of the Western hemisphere learned the use of tobacco from the native Indians and introduced the tobacco habit into Europe. The use of tobacco for smoking, mastication or snuffing is indulged in by many millions of people throughout the world.

Chemical Composition of Tobacco. Nicotine is the most important pharmacological constituent of tobacco. The percentage of nicotine in tobacco varies considerably and may range from 0.5 to 8.0 per cent. Cigarette tobacco contains about 1.5 per cent (0.7 to 3.0 per cent) of nicotine and the smoke of the average cigarette may yield several "therapeutic" doses of nicotine (six to eight mgm). The smoke of 100 grams of cigar may contain from 150 to more than 400 mgm of nicotine. The amount of nicotine contained in tobacco smoke depends on many factors. Nicotine is present in the tobacco leaf as the salt of organic acids and is liberated by heat to the free form, which passes in varying degree into the smoke. Some of the alkaloid is burned but appreciable quantities, depending on the moisture, heat, rapidity of smoking, practice of inhalation, etc., gain access to the respiratory tract. Not all of this is absorbed because most of it is again exhaled or expectorated. Most commercial "denicotinized" tobaccos still contain significantly large amounts of the alkaloid.

In addition to nicotine, tobacco contains pyridine and other nitrogenous bases, volatile acids, tarry and phenolic substances, and especially furfural and acrolein. These chemicals undoubtedly contribute, along with free nicotine, to the irritation of the mucous membranes produced by tobacco and tobacco smoke (Bogen, 1936). Carbon monoxide and hydrocyanic acid are present in tobacco smoke in too low a concentration to be significant. Hygroscopic agents, such as glycerol, may add to the irritant effects of tobacco smoke, probably due to their yield of acrolein. Insecticidal sprays used on domestic tobacco plants may result in lead and arsenic contents of cigarettes far in excess of those limits allowed by law for foods (Ziedler and Wagner, 1937). Although lead and arsenic are potentially more harmful when volatilized and inhaled than when ingested orally, there is no absolute evidence as yet that toxic effects of tobacco are caused by the content of these metals. This question, however, deserves closer study in view of some questionable cases of arsenical dermatitis reported from the use of tobacco.

Chronic Effects of Tobacco. The acute effects of smoking in the novice are almost entirely due to the nicotine content of the tobacco. These have been described under nicotine intoxication. The symptoms, though unpleasant, are transitory and not alarming. The chronic use of tobacco by a large part of our population raises the problem of the *chronic toxicity* of nicotine. Many symptoms and diseases have been blamed at one time or another on the use of tobacco. Despite the vast amount of work done, it has not been established that the moderate use of this plant is deleterious to the overwhelming number of persons who indulge in the tobacco habit.

Nasopharyngeal and bronchial irritation may occur from tobacco smoking. This is due not only to the causticity of nicotine but, as has been stated, to the many other irritant constituents of the tobacco or its smoke. Mucosal epitheliomas may also result from the chronic irritation of tobacco and heat.

The effects of tobacco smoking on the motor and secretory activities of the *gastro-intestinal tract* have been carefully studied by Schnedorf and Ivy (1939) in chronic cigarette smokers, nonsmokers and smokers with peptic ulcer. They found that cigarette smoking reflexly stimulates *salivary secretion* by virtue of the irritant smoke and not because of the nicotine. The subcutaneous injection of 0.4 mgm of nicotine (the amount of alkaloid that may be absorbed by smoking two cigarettes) does not stimulate salivary flow. *Hunger contractions* of the stomach in man are reflexly abolished by smoking and the inhibition caused by smoking one cigarette may last for 15 to 60 minutes. The gastric *emptying time* of a test meal is not significantly altered by tobacco smoking in chronic smokers, but the gastric acidity may be reduced. In smokers with peptic ulcers, neither the rate of emptying nor acidity of the gastric contents is influenced by cigarette smoking. The experimental data are summarized in Table 27. The volume and acidity of the continuous fasting gastric secretion were also studied by Schnedorf and Ivy. In only one of 40 normal subjects were the volume and acidity enhanced; in 17, no significant alteration occurred and in 22 an appreciable decrease took place. In only one of 20 patients with peptic ulcer (a nonsmoker) was the acidity of the basal gastric secretion augmented; in eight, no significant change occurred, and in 11 subjects a decrease was noted.

These results offer no basis for the opinion held by many clinicians that cigarette smoking is harmful to patients with gastric or duodenal ulcer. The gastro-intestinal com-

Table 27

EFFECT OF SMOKING ON THE EMPTYING TIME AND ACIDITY OF THE GASTRIC CONTENTS IN CHRONIC SMOKERS AND IN PATIENTS WITH ULCER WHO SMOKED *

(Schnedorf and Ivy, 1939).

Subjects	Control No Smoking			On Smoking 3 or 4 Cigarettes		
	Volume Recovered, cc.	Acidity, Chlorine Units		Volume Recovered, cc.	Acidity, Chlorine Units	
		Free	Total		Free	Total
Chronic smokers without ulcer (7)†	63	33	54	67	20	37
Smokers with ulcers (22)‡	92	52	62	92	50	61

* Saliva was not swallowed. A bouillon test meal with three crackers was used. Three or four cigarettes were smoked in one hour.

† Two showed a slight but significant retention; the acidity was significantly diminished in four.

‡ In one a significant retention occurred with smoking. In no instance was the rate of evacuation significantly lessened.

plaints sometimes caused by the use of tobacco may be secondary to cardiovascular disturbances. Unless it can be shown definitely in a particular patient with peptic ulcer that the use of tobacco is harmful, it is not necessary to proscribe smoking. The chronic user of tobacco experiences a certain pleasure and euphoria which may facilitate the digestive processes. Patients with ulcer, however, should be warned not to tax their tolerance for tobacco by overindulgence.

Schnedorf and Ivy also examined the claims that smoking augments the motor activity of the colon and that the cigarette indulged in after breakfast by many individuals to promote defecation has a pharmacological basis. They found in a systematic experimental study that smoking tended to increase the motor activity of the colon. It is possible that certain patients with colitis or irritability of the colon may benefit from restriction of the use of tobacco.

Considerable attention has been focused on the effects of tobacco on the *cardiovascular system.* In certain patients, the excessive use of tobacco may cause premature systoles and in an occasional person paroxysmal attacks of auricular tachycardia may be traced to smoking. In some individuals, tobacco smoking may produce an inversion of the T wave (Graybiel, Starr and White, 1938). There is no proof that the use of tobacco causes arteriosclerosis or results in angina pectoris (White and Sharker, 1934). In a patient who already has coronary sclerosis and angina pectoris, however, it is conceivable that overindulgence in tobacco may be a factor in precipitation of anginal attacks. This can be determined only by individual study of each patient and does not justify the indiscriminate interdicting of tobacco in persons with angina pectoris. The use of tobacco apparently plays no rôle in initiating *coronary thrombosis* (Master and coworkers, 1937).

The use of tobacco has long been suspected of being etiologically related to *Buerger's disease,* but the exact connection is far from clear. More than 90 per cent of all patients with thromboangiitis obliterans are smokers. Some authorities even claim that no instances of typical and unquestionable Buerger's disease have occurred in nonsmokers. The disease is apparently less severe and more amenable to therapy in those patients who give up smoking early and completely, at least so far as is indicated by the incidence of amputations (Horton, 1938; Silbert, 1938). Although nicotine is known to produce vasospastic phenomena, this fact does not prove that tobacco is the causative agent rather than an important contributory factor in the disease. Most clinicians are of the opinion that a patient with Buerger's disease should stop smoking completely, and that the continuance of the use of tobacco will tend to make the symptoms worse. In a large series of cases, Silbert (1938) observed no recurrence of the syndrome, once arrested by treatment, unless the patient resumed smoking. The rôle of tobacco in vasospasm and in the etiology of thromboangiitis obliterans has been reviewed by Moyer and Maddock (1940).

Tobacco amblyopia is a relatively rare complication of the tobacco habit. It is usually characterized by retrobulbar neuritis and if untreated may proceed to optic atrophy and permanent visual injury. Complete cessation of the use of tobacco is indicated in tobacco amblyopia, and vasodilators such as nitrites and choline esters, especially mecholyl, should be employed in therapy (Orr, 1936; Duggan, 1937). The evidence strongly suggests that spasticity of retinal vessels induced by nicotine provides the underlying basis for this syndrome.

The smoking of tobacco under controlled conditions of a standard smoking test is known to produce *peripheral vasoconstriction,* especially in the skin, in the vast majority of persons, regardless of whether they are healthy or suffering from vascular disease, and independently of the length of time tobacco has been used. The vasoconstriction is accompanied by a marked fall in skin temperature (Hines and Roth, 1938). The majority of individuals also respond to cigarette smoking with a rise in both *systolic and diastolic blood pressure,* and the rise is more marked in those who have essential hypertension. Excessive elevation of blood pressure induced by tobacco is noted especially in those persons who have inherently hyper-reactive vascular systems, as measured by the cold pressor test (Herrel and Cusick, 1938; Hines and Roth, 1938). The extent of these blood pressure changes can be seen in Table 28, compiled by Hines and Roth. This evidence, however, does not indicate that tobacco must not be used by hypertensive patients or by those with peripheral vascular disease (except Buerger's). Each patient should be studied to determine whether a moderate amount of smoking is harmful in his case.

Experimental results in animals do not indicate that the chronic use of nicotine causes vascular degeneration (Thienes and Butt, 1938), nor do reasonable amounts of the alkaloid affect general health or growth (Behrend and Thienes, 1932). Pearl (1938) investigated the effect of tobacco smoking on the length of life of nearly 7000 white males. While heavy smoking definitely impaired life duration, mild smoking only slightly decreased life expectancy. Should the conclusions of Pearl's study be substantiated (Short, Johnson and Ley, 1939), one would still have to weigh the pleasures derived from tobacco against the possibility that the life span may be decreased in a given case. Pearl noted that after the age of 70 the differences between the groups practically disappear, and suggests that those "who survive to 70 or thereabouts are such tough and resistant specimens that thereafter tobacco does them no further measurable harm as a group."

Table 28

RESPONSE OF BLOOD PRESSURE TO STANDARD SMOKING TEST AND COLD PRESSOR TEST

Classification of Subjects	Number	Mean Change in Blood Pressure, Mm. of Mercury					
		smoking test		control test*		cold test	
		Systolic	Diastolic	Systolic	Diastolic	Systolic	Diastolic
Normal blood pressure	30	21.1	13.0	4.2	−1.0		
Normal reactors to cold test......	20	17.2	7.6	2.8	−2.1	13.6	9.5
Hyper-reactors to cold test......	10	29.6	17.4	9.3	1.6	33.2	25.0
Essential hypertension	56	31.5	18.4	10.6	5.6	44.5	37.7
Smokers..........	45	40.9	23.0				
Nonsmokers.......	11	26.0	9.3				

* Puffing unlighted cigarette.
Hines and Roth, 1938.

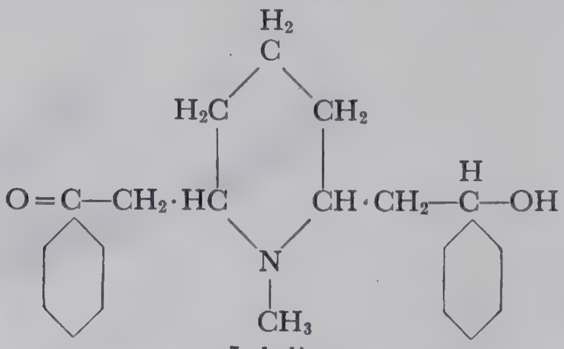
In *summary,* it may be stated that each patient must be studied carefully in an attempt to decide whether in his case tobacco is producing chronic intoxication. Although tobacco is contraindicated in Buerger's disease and in nicotine amblyopia, no generalities can be stated regarding the deleterious effects of smoking on patients with other disease syndromes. It is unfair and often unnecessary to request one to give up smoking, unless the evidence is of a much more convincing nature than that usually advanced.

The tobacco habit is not particularly easy to break. Although Mark Twain is recorded as saying that to cease smoking was the easiest thing he ever did, he hastened to add that he ought to know because he had done it a thousand times. The abstinence symptoms are mainly psychic (craving, restlessness, etc.) and do not have the profound constitutional basis as do those occurring in narcotic addicts. Often it is necessary only to decrease the amount of tobacco used or the degree of inhalation rather than to interdict smoking completely. The use of lobeline in tobacco withdrawal is discussed under that alkaloid.

LOBELIA

Lobelia, N.F., B.P. (Indian tobacco), is obtained from the dried leaves of an herb, *Lobelia inflata.* It was used in American medicine in the 19th century as an emetic, nauseant, expectorant and antiasthmatic. An alkaloid, *lobeline,* is the chief constituent of lobelia, and it was first obtained in crystalline form by Wieland in 1915 and named "alpha-lobeline."

Chemistry. The structural formula of lobeline is as follows:



Lobeline

Lobeline is usually available as the sulfate salt. The other alkaloids of lobelia are similar to lobeline in action but are weaker. The *tincture of lobelia* (N.F., B.P.) and *fluidextract of lobelia* (N.F.) are also available.

Pharmacological Properties. Lobeline has essentially the same actions in the body as nicotine. Indeed, animals tolerant to nicotine show cross-tolerance to lobeline. The drug stimulates the *central nervous system* and this effect is especially evident for the medullary, respiratory, and vomiting mechanisms. Central vagal stimulation may result in bradycardia, hypotension and bronchial constriction. Like nicotine, the alkaloid stimulates the chemoreceptors in the carotid body and thus reflexly increases respiratory rate and depth (Heymans and associates, 1931).

The *ganglionic actions* of lobeline consist of a primary stimulation followed by depression. The drug also has a curare-like action on *skeletal muscle*. The *cardiovascular* effects of lobeline are complicated and essentially similar to those of nicotine. Conduction disturbances occur due to a direct action of the alkaloid on the myocardium. The drug also causes a discharge of epinephrine from the adrenal medulla.

Preparations. Both alpha-lobeline and lobeline sulfate are marketed but neither preparation is official or Council-accepted. The alleged superiority of alpha-lobeline as a respiratory stimulant over other lobeline preparations has not been substantiated. The drug has been administered orally and parenterally.

Therapeutic Uses. Lobelia and its galenical preparations are obsolete in modern medicine. Lobeline, however, has been used as a *respiratory stimulant,* and has been given extensive trial in resuscitation of the new-born and in cases of poisoning by central depressant drugs. The hypodermic dose for adults is from three to 10 mgm. The efficacy of the alkaloid as a respiratory stimulant and analeptic, however, is rather capricious and variable. At best, the salutary effects of lobeline are brief in duration. Medullary excitation often involves the emetic center, and the action on the central vagal nuclei may result in a fall in blood pressure and slowing of the heart rate. The dose necessary to produce respiratory stimulation varies greatly from patient to patient and with the condition being treated. Brief benefit may be followed by even more pronounced depression. Indeed, improvement may fail to appear. A fall in blood pressure is likely to occur especially when the subject is deeply narcotized. The early enthusiastic clinical reports on the value of lobeline as a respiratory stimulant and analeptic have not been substantiated and the drug is too dangerous and uncertain in action to warrant its employment in preference to more effective and safe therapeutic agents.

Because of the cross-tolerance which exists between nicotine and lobeline, the latter drug has been proposed for the *control of the tobacco habit.* It is taken orally in capsules containing eight mgm of lobeline sulfate, the dose being repeated as necessary during the day to control acute withdrawal symptoms. A week of gradually decreasing use of the drug is said to be generally sufficient (Dorsey, 1936). Wright and Littauer (1937), however, report that lobeline sulfate employed to break the tobacco habit may cause faintness, vomiting, epigastric pain and anorexia, and that most patients express a desire to give up smoking without the help of the substituted drug.

CURARE

Curare is an important pharmacological tool for laboratory investigations, but as yet it has no well-established therapeutic uses. The drug is an extract of the barks of several species of *Strychnos* plants and is employed by the South American Indians as an arrow poison. Synonyms for this extract include *curara, urari,* and *woorari.* Despite the fact that curare was first brought to England by Sir Walter Raleigh in the latter part of the 16th century, systematic investigation of the drug was first undertaken in 1850 by Pelouze and Claude Bernard. Although curarine was isolated in crystalline form by Preyer in 1864, even today much remains to be learned concerning the chemical nature and pharmacological actions of this powerful alkaloid. After prolonged and intimate study of the South American Indian methods of preparing curare, Mr. Richard C. Gill has been able to learn the technic of manufacture of the drug by the natives and has brought to the United States a sufficient amount of authentic curare for extensive experimental investigation (Gill, 1940).

Chemical Composition. Curare is obtained by brewing the stems, roots, bark and leaves of several species of *Strychncs.* Commercial curare is a brownish or black shiny, resinoid mass, soluble in cold water and dilute alcohol. Reliable curare extracts are difficult to obtain and the commercial supplies are often unsatisfactory. The active principles in curare are alkaloids, but their chemical structures remain unknown. The alkaloids differ in each variety of curare and these varieties are usually designated by the containers in which they are supplied to importers. Thus, there are three types of curare—that in bamboo tubes is known as *tubocurare;* that in gourds is called *calabash curare* (from *Strychnos toxifera*); and that supplied in earthenware jars is named *pot curare.*

Tubocurare is the most common form of extract but its source is undetermined. It contains two alkaloids, *tubocurarine* which possesses the main characteristics of the crude drug, and *curine* which is much weaker. Calabash curare is the most desirable extract and yields *curarine,* an extremely potent alkaloid similar to tubocurarine, and related chemically to strychnine. Pot curare contains three alkaloids, only one of which, *protocurarine,* has typical curariform properties.

The chemical basis for curariform activity of drugs is not known. At present, it appears that this property is independent of detailed chemical structure. Many onium salts, for example, possess curare-like potency in addition to nicotinic and muscarinic activity (Ing, 1936). These include quaternary ammonium salts, simple phosphonium, arsonium, stibonium, sulfonium and iodonium salts, and the methochlorides of several alkaloids, such as quinine methochloride (Harvey, 1940).

Mechanism of Action. Curare is an autonomic blocking agent which acts mainly on skeletal muscles and to a lesser degree on autonomic ganglia. It prevents these structures from responding either to nerve impulses or to injected acetylcholine. Brown and coworkers (1936) have shown, however, that small doses of curarine block the response of skeletal muscle to injected acetylcholine more readily than the response to a motor nerve volley. In this respect, the autonomic blocking action of curare on skeletal muscle resembles that of atropine on certain smooth muscles (page 340). This inhibition of response is due to a direct action on the cell. The release of acetylcholine by impulses in preganglionic autonomic fibers to ganglia and by somatic motor nerve impulses to voluntary muscles is not prevented by curare but the response to the chemical mediator is blocked. The selective blocking of ganglionic transmission and of neuromuscular junctions is not due to a paralytic action of curare because the involved cells are still capable of responding to other forms of stimuli. Thus curarized ganglion cells can be discharged by potassium salts and skeletal muscle fibers can be made to contract by direct electrical stimulation. Curare also exhibits its typical effects on structures whose nerves are completely degenerated. The choline esters, physostigmine and prostigmine are pharmacological antagonists to curare in their stimulatory phase of action on ganglia and skeletal muscles.

The action of curare does not extend to structures innervated by postganglionic autonomic fibers, and thus smooth muscle and gland cells are not affected directly. By acting on skeletal muscles and ganglia, curare blocks the "nicotinic" actions of acetylcholine. Curare shares its specific autonomic properties with nicotine but differs from this latter alkaloid in three important respects. Curare has a much less pronounced effect on ganglia than has nicotine; it lacks the initial stimulatory phase of the action of nicotine; and finally curare does not have the ability specifically to stimulate respiration as does nicotine.

Pharmacological Properties. The action of curare on skeletal muscle is the basis for the outstanding effects of the alkaloid in the mammalian body. The peripheral locus of this action was first described by Claude Bernard in his classical investigations which have become the basis for the experiment on drug localization performed today by medical students in the pharmacological laboratory. If the hind leg of a frog is ligatured in a manner which deprives the limb of its circulation but allows the sciatic nerve to remain free, the injection of curare into the ventral lymph sac produces typical effects in all parts of the frog except in the ligatured limb. In this limb, electrical stimulation of the sciatic nerve produces typical muscular contraction whereas the opposite limb is unresponsive to nerve stimulation. It is thus clear that curare does not act centrally but must reach the periphery before it can exert its action. Further localization is accomplished by showing that the curarized muscle is electrically excitable when stimulated directly and that the sciatic nerve, soaked in a solution of curare, is still capable of carrying impulses. This places the site of action at the motor end-plate or neuromuscular junction.

Curare also blocks transmission of impulses in autonomic ganglia but this property is not as marked as with nicotine. The ultimate effects of this action on any particular organ depend upon whether the sympathetic or parasympathetic ganglia are more markedly affected. Ordinarily, death from paralysis of the respiratory muscles occurs before the ganglionic action is fully developed.

Curare stimulates the central nervous system. Strychnine-like convulsions are seen after the use of some samples of curare, and picrotoxin-like spasms after others. Ordinarily, however, convulsions are masked by the peripheral muscular depression.

Curare Poisoning. A curarized muscle first shows fatigue and weakness, and as poisoning continues it becomes totally flaccid and inexcitable. An animal, poisoned by this alkaloid, ultimately lies perfectly helpless and dies from asphyxia when the muscles of respiration are involved. The muscles of the fingers, toes, eyes and ears are affected first, then those of the limbs, neck and trunk and finally those of the diaphragm. Asphyxial convulsions do not occur because of the inability of the muscles to contract. Cardiac failure results from anoxia following the respiratory arrest, and not from a direct toxic action of curare on the heart. Consciousness and sensibility are retained until the end. Life can be saved by artificial respiration because curare is fairly rapidly destroyed and excreted by the organism. Recovery of muscles occurs in the reverse order to that of their paralysis and thus the diaphragm and intercostal muscles are first to recover their function.

The intravenous injection of curare in man (Bennett, 1940) results in immediate onset of effects. First, there is a feeling of heaviness of the eyelids, followed by bilateral ptosis, slight nystagmus, strabismus, and diplopia. The neck muscles are soon affected and the subject is unable to raise his head; facial expression is quickly lost, speech is slow, and the throat and jaw muscles then become flaccid. The spinal muscles are next involved and lastly there occurs complete paralysis of the arms and legs. The order of involvement of the skeletal muscles by curare is the same as that which occurs in a patient with progressive myasthenia gravis. After intramuscular injection, the effects of curare require 15 minutes to become evident.

Absorption, Fate and Excretion. Although the South American Indian may kill his game with blow darts poisoned with curare, the meat of the kill can be eaten with impunity. Evidently, gastro-intestinal absorption of curare is sufficiently limited so that the processes of detoxication and excretion prevent a toxic level of curare from accumulating in the tissues. It is also possible that the drug may be destroyed in the intestinal tract. Small hypodermic doses of curare are therefore more effective than large amounts taken orally. Thus, the drug may be sucked from a wound without danger provided there is no extensive ulceration of the mouth or enteric tract. Curare is partly destroyed by the liver and the remainder is eliminated unchanged by the kidney. An otherwise harmless dose of the drug may become toxic in the presence of impaired renal function.

Clinical Uses. Curare and its alkaloids have no valid, well-established clinical uses. Sporadic attempts have been made to employ curarine in tetanus, strychnine poisoning and other convulsive states, as well as in neuromuscular syndromes characterized by increased muscular movement, tone or rigidity such as spastic paraplegia, dystonic athetosis and advanced parkinsonism. Aqueous or alcoholic extracts of curare have also been injected parenterally in doses sufficient to produce generalized muscular flaccidity in order to protect patients receiving convulsive (metrazol) shock therapy for schizophrenia from developing traumatic fractures (Bennett, 1940). A major difficulty in the use of curare is to obtain that degree of action which will just permit the desired decrease in skeletal muscle activity without interfering with respiration (*see* Cole, 1934; Mitchell, 1935; West, 1936).

The most favorable therapeutic results obtained thus far are those reported by Burman (1939, 1940) in 19 patients with *spastic paralysis* and in several cases of *dystonia musculorum deformans*. The dose of the curare employed was variable, and ranged from 10 to 40 mgm given intramuscularly to 22 to 25 mgm given intravenously. Although the drug appeared to be excreted rapidly (within two hours), the beneficial effect generally lasted one or two days, occasionally longer. Injections were therefore given three times weekly. Benefit was noticeable immediately after intravenous administration of the curare, and 20 to 30 minutes after intramuscular injection. Apparently only spastic muscles are affected by the doses of alkaloid employed, because normal muscles and respiratory movements remained unimpaired. Repeated therapy did not cause harmful effects and tolerance did not develop. Untoward symptoms observed with larger amounts than were needed to improve spasticity included dizziness, diplopia, weakness, ataxia, etc., but no difficulty in breathing was noted. The symptoms lasted only 15 to 30 minutes. The results seemed to indicate distinct improvement in spasm and plastic muscular rigidity. In dystonia musculorum deformans, a bedridden patient may be made to walk again. Burman also reported good results in *torticollis.* In an effort to find a curare substitute, *erythroidine hydrochloride,* derived from the seeds of *Erythrina corralloides,* was tried in five patients, in only two of whom satisfactory results were obtained owing to the small amount of drug available. Erythroidine seems to be more active, less toxic, safer, and more easily prepared and assayed than curare. The dose is larger than for curare. The interesting experiments of Burman deserve repetition, and their corroboration is greatly to be desired.

Curare is used in the laboratory to produce immobility of animals without central nervous system paralysis, but it does not produce anesthesia.

NICOTINE AND LOBELINE

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SECTION VI

CARDIOVASCULAR DRUGS

A large number of drugs have as their major pharmacological action the ability to stimulate or depress the heart, or to constrict or dilate the blood vessels. These agents will be considered in this section. Many additional drugs, however, which also markedly influence the cardiovascular system are described elsewhere in connection with their other important pharmacodynamic properties. This second group includes the xanthines, the central nervous system stimulants, parasympathomimetic and sympathomimetic drugs, the belladonna alkaloids, nicotine, the ergot alkaloids, thiamine, thyroid, posterior pituitary, carbon dioxide, and numerous other agents.

CHAPTER 28

DIGITALIS AND ALLIED CARDIAC GLYCOSIDES

Digitalis and certain closely allied drugs have in common a specific and powerful action on the myocardium which is unrivaled in value for the treatment of heart failure. These cardiac drugs are mainly found in a number of plants but are also present in the cutaneous secretions of certain toads. The preparations commonly employed are obtained from digitalis, strophanthus or squill. In the following discussion, the terms *digitalis principles, cardiac glycosides* and *digitalis bodies* are used to designate the entire group rather than digitalis alone. The description of the pharmacology and uses of digitalis applies to all related cardiac glycosides unless otherwise stated.

History. A large number of plant extracts containing cardiac glycosides have been used by natives in various parts of the world as arrow and ordeal poisons. Squill was known as a medicine to the ancient Egyptians and is mentioned in the Ebers Papyrus (*circa* 1500 B.C.). The Romans employed it as a diuretic, heart tonic, emetic and rat poison. Strophanthus was introduced into medicine by Sir Thomas Fraser (1890) who discovered its digitalis-like action while studying African arrow poisons. A drug which has been used for centuries by the Chinese is the dried skin of the common toad. It is called Ch'an Su and is recommended especially for toothache and bleeding of the gums. The latter use is interesting because it long preceded the demonstration that the toad skin contains a high percentage of epinephrine, a local hemostatic. Powdered toad skins were also commonly employed in the folk medicine of western countries for dropsy until replaced by digitalis.

Digitalis or foxglove was mentioned in 1250 in the writings of Welsh physicians. It was described botanically 300 years later by Fuchsius (1542) who gave it the name *Digitalis purpurea* because the flower was purple and resembled a finger. Foxglove was occasionally used internally or locally for a number of unrelated diseases ranging from epilepsy to skin ulcers.

In 1785, William Withering, master physician and botanist of Birmingham, England, published his famous book entitled, "An Account of the Foxglove and Some of its Medical Uses." Every physician who uses digitalis would do well to read this scholarly work because many of the common errors current in digitalis medication were clearly anticipated and warned against by Withering. He tells how he came to use foxglove, 10 years before he published his results, as follows, "In the year 1775, my opinion was asked concerning a family receipt for the cure of the dropsy. I was told that it had long been kept a secret by an old woman in Shropshire, who had sometimes made cures after the more regular practitioners had failed. I was informed also, that the effects produced were violent vomiting and purging; for the diuretic effects seem to have been overlooked. This medicine was composed of twenty or more different herbs; but it was not very difficult for one conversant in these subjects, to perceive, that the active herb could be no other than the Foxglove."

Withering was conversant with the fact that digitalis was effective only in certain forms of dropsy but apparently did not associate this with the cardiac actions of the drug. He recognized that the heart was affected, however, for he wrote that, "It has a power over the motion of the heart to a degree yet unobserved in any other medicine, and this power may be converted to salutary ends." Apparently John Ferriar in 1799 was the first to ascribe to digitalis a primary action on the heart and to relegate the diuretic effect to a secondary rôle.

Whereas Withering knew and recorded the benefits to be derived from the proper use of foxglove, his advice was not always heeded. During the 19th century, digitalis was used indiscriminately, often in toxic doses, for many disorders. During the early 20th century, as a result of the work of Cushny, Mackenzie, Lewis and others, the drug gradually came to be looked upon as a specific in the treatment of auricular fibrillation. Only within the last 20 years has it become firmly established that the main value of digitalis is in the therapy of congestive heart failure.

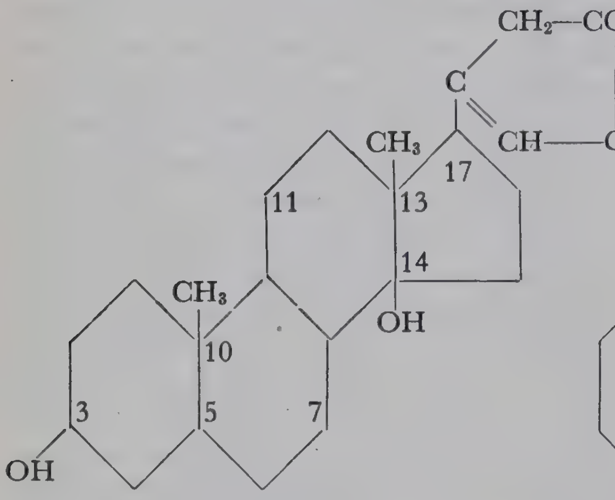
Source and Composition of the Digitalis Principles. Official digitalis is the dried leaf of the common and beautiful foxglove plant, *Digitalis purpurea,* a flowering biennial indigenous in many parts of the United States. The seeds and leaves of a number of other digitalis species also contain active cardiac principles. The official *strophanthus* is obtained from the seeds of the *Strophanthus kombé* or *hispidus,* members of the *Apocyanaceae* family. Other species of *Strophanthus* also contain active cardiac glycosides, and *ouabain* is derived from *Strophanthus gratus.* Official *squill,* the dried fleshy bulb of the "sea onion," comes from the *Urginea* (*Scilla*) *maritima,* a species of *Liliaceae.* Another member of this same family, *Convallaria majalis* (lily of the valley) was used for years in Russia for dropsy and yields a cardiac glycoside, *convallatoxin,* which is not now used clinically but possesses characteristic digitalis action. Belonging to the same family as the *Strophanthus* plant is a tropical tree, *Thevetia neriifolia* (yellow oleander) which produces a fruit known as the bestill or Malayan nut. The kernel of this nut yields the glycoside *thevetin* which has had some clinical trial (Arnold, Middleton and Chen, 1935). Many other plants contain cardiac glycosides but they are not listed here because their clinical value has not yet been fully established.

The active constituents of these cardiac drugs are *glycosides.* The cardiac glycosides of plant origin are usually found with *saponins.* The saponins are also glycosidic substances but lack specific effects on the heart. The best known saponins of the digitalis group are digitonin and gitonin. Although present in galenical preparations, the saponins exert no therapeutic activity but rather affect the solubility of the cardiac principles.

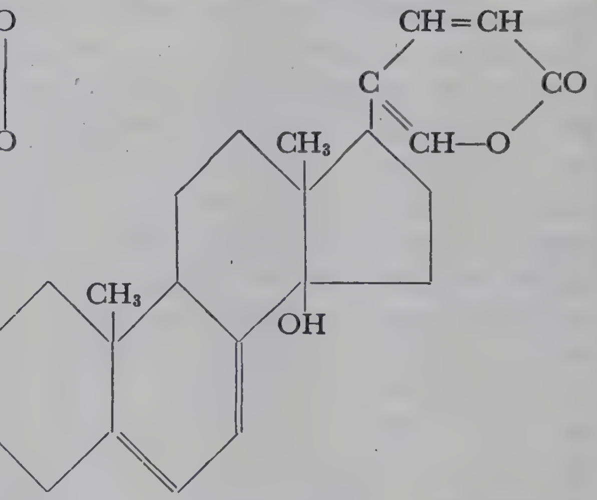
The numerous cardiac glycosides are composed of several constituent parts. Each glycoside represents the combination of an *aglycone* or *genin* with one or more molecules of sugar (Table 29). The pharmacological activity resides in the aglycone; but the particular sugars to which the aglycone is attached are thought to control water-solubility, cell penetrability, and persistence of cardiac action —hence, the therapeutic potency of the molecule. For example, the sugars are inactive when given alone, but when linked to aglycones the potency and toxicity of the latter are increased severalfold. The sugars are monosaccharides. Some of them are well known, such as glucose and rhamnose. Others, such as digitoxose and digitalose, are unusual pentose sugars which are found only in digitalis principles and are unlike any known sugars. The same sugar may occur in linkage with different aglycones. Likewise, different glycosides may yield on hydrolysis the same aglycone. For example, the glycosides of Canadian hemp (cymarin) and the seeds of *Strophanthus kombé* (k-strophanthus-β) both contain the aglycone *strophanthidin* (Table 29).

Chemical Nature of the Cardiac Aglycones. Rapid advances have been made in recent years in the complicated chemistry of the cardiac aglycones. Among the many contributions to this interesting field, the work of Jacobs, Windaus, Stoll, Fieser and their respective associates are outstanding and reference should be made to their publications for details. From the standpoint of the clinician, however, the swift development of this field of research has not yet resulted in information which is very helpful in therapeutics. For this reason, the following discussion is only a brief outline of the salient features.

The aglycones can be released from the cardiac glycosides either by acid or enzymatic hydrolysis. Their complex structure was but poorly understood until it was discovered that they are chemically related to the bile acids, cholesterol, sterols and sex hormones. The basic structure is a cyclopentenophenanthrene nucleus to which is attached a lactone ring. In addition, certain methyl, hydroxy and aldehyde groups are attached in specific positions, varying with the particular aglycone. The empiric formula, as a rule, is $C_{23}H_{34}O_{(4-8)}$. The structural formulas of two aglycones, *digitoxigenin* and *scillaridin-A,* are included here in order to demonstrate the characteristic features of these potent cardiac drugs.



Digitoxigenin



Scillaridin-A

Other important aglycones differ from those aforementioned in minor ways. For example, *gitoxigenin,* which is found in digitalis leaves with digitoxigenin, differs from the latter only in having an hydroxy group attached to C_{16}. *Strophanthidin* differs from digitoxigenin only by virtue of an hydroxy at C_5 and an aldehyde group at C_{10} instead of a methyl radicle. *Digoxigenin,* a third digitalis aglycone found in the *Digitalis lanata* species, has the same carbon skeleton but the position of a third hydroxy group has not been definitely assigned. The glycoside obtained from *Strophanthus gratus* is *ouabain,* a crystalline substance. The aglycone which it yields is called *ouabagenin,* the skeletal structure of which differs from digitoxigenin in having a CH_2OH group instead of CH_3 on C_{10}, and hydroxy groups on C_7 and C_{11} (Fieser and Newman, 1936). *Scillaren-A,* an important glycoside of *Squill,* yields the aglycone *scillaridin-A* which differs from the aglycones of the digitalis-strophanthus group in having an extra C atom. This carbon is in the lactone ring which therefore makes scillaridin-A the intermediate link between the cardiac principles and the bile acids.

The essential features of the sources and component chemical parts of the major cardiac glycosides are summarized in Table 29. A special indication for such a summary exists in the fact that the terminology employed in the literature is confusing and awkward, particularly because the names refer not to chemical structures but rather to botanical origins. Table 29 shows that the leaves of *D.*

TABLE 29

SOURCE AND COMPONENT CHEMICAL PARTS OF THE MAJOR CARDIAC GLYCOSIDES

SOURCE		GLYCOSIDE*	SUGAR	AGLYCONE
Digitalis purpurea	Leaves	deacetyldigilanid A −glucose = digitoxin	3 digitoxose	digitoxigenin
		deacetyldigilanid B −glucose = gitoxin	3 digitoxose	gitoxigenin
		gitalin	2 digitoxose	gitaligenin
	Seeds	digitalin**	glucose and digitalose	dianhydrogitoxigenin (digitaligenin)
Digitalis lanata	Leaves	digilanid A $-\begin{cases}\text{glucose}\\ \text{acetyl}\end{cases}$ = digitoxin	3 digitoxose	digitoxigenin
		digilanid B $-\begin{cases}\text{glucose}\\ \text{acetyl}\end{cases}$ = gitoxin	3 digitoxose	gitoxigenin
		digilanid C $-\begin{cases}\text{glucose}\\ \text{acetyl}\end{cases}$ = digoxin	3 digitoxose	digoxigenin
Strophanthus S. sarmentosus		sarmentocymarin	sarmentose	sarmentogenin
S. gratus		ouabain	rhamnose	ouabagenin
S. kombé		k-strophanthin-β (strophanthin)	glucose and cymarose	strophanthidin
		k-strophanthoside	2 mol. glucose and cymarose	strophanthidin
Apocyanum (Canadian hemp)		cymarin	cymarose	strophanthidin
Squill		scillaren A	glucose and rhamnose	scillaridin A
Thevetia neriifolia (Be-still nut)		thevetin	glucose (2 mol.) and digitalose (?)	thevetigenin

Compiled from data presented by Fieser (1937) and Stoll (1937, 1939).

* The digilanids and deacetyldigilanids are "native" glycosides as they are supposed to occur in the plant.

** Not the commercial "digitalin."

purpurea and *D. lanata* yield the glycosides digitoxin and gitoxin, but that each species in addition contains a glycoside not possessed by the other. Stoll (1937) showed that these glycosides exist in the plants as precursors, called native glycosides. In the case of *lanata* leaves the precursors are termed digilanids A, B and C, which upon mild alkaline hydrolysis (loss of acetyl group) and enzymatic hydrolysis (loss of glucose) yield the glycosides digitoxin, gitoxin and digoxin respectively. Further acid hydrolysis splits off the peculiar pentose sugars mentioned above and yields the aglycones. In *purpurea* leaves, however, the precursors or native glycosides contain no acetyl groups and no analogue of digilanid C.

They are known as deacetyldigilanids A and B, which upon enzymatic hydrolysis yield digitoxin and gitoxin. In addition, this species has the glycoside *gitalin* which is not present in the lanata leaf.

Relationship Between Chemical Structure and Cardiac Action. In the discussion of the opium alkaloids of the phenanthrene series, it was pointed out in detail how slight alterations in the morphine molecule resulted in specific and marked changes in pharmacological actions. In regard to the cardiac aglycones, however, no such discrete correlation exists. So far as is now known, all the aglycones mentioned above produce the same type of cardiac effect. It is possible, therefore, only to suggest the features of the molecular structure which are essential for this activity.

Practically all the cardiac aglycones have a secondary OH group in the C_3 position characteristic of the sterids, but a particular stereochemical configuration at C_3 is thought necessary for the cardiotonic effect. For example, the very weak action of *uzarin* is probably connected with the lack in this aglycone of the characteristic OH configuration in the C_3 position. The number and position of the other hydroxyls are probably unimportant except for determining solubility. The unsaturated lactone ring is absolutely essential for the myocardial effects of cardiac aglycones. Saturation of the ring destroys both potency and toxicity. Opening of the ring similarly abolishes pharmacological activity of the molecule. Whether the unsaturated lactone ring attached to other skeletons than the cyclopentophenanthrene nucleus would manifest cardiac activity remains to be demonstrated. The interested reader is referred to Jacobs (1933), Elderfeld (1935), Fieser (1937) and Stoll (1937) for details of the chemistry of the cardiac glycosides.

Cardiovascular Actions of Digitalis Principles

The main systemic effects of digitalis and allied cardiac drugs are manifested on the cardiovascular system. In addition, digitalis has some actions on the nervous system. An analysis of the actions of digitalis on the cardiovascular system is complicated by the multiple and interrelated functions controlling the circulation and also by the fact that digitalis elicits different responses in health and in disease. Another disturbing feature is that practically nothing is known of the basic mechanism whereby digitalis affects heart muscle. There is no question that cardiac muscle is much more sensitive to cardiac glycosides than are other muscles of the body. It also appears that the glycosides enter the cell protoplasm and are there split to release the active aglycones. How the latter cause such remarkable changes in muscular contraction is a mystery. The following description, therefore, is limited to observed facts rather than to the explanation of how digitalis causes the heart muscle to beat more forcibly. Wherever possible, these facts are taken from clinical investigations.

Action of Digitalis on Heart Muscle. The myocardial action of digitalis is its most important pharmacodynamic effect. Most of the changes in cardiovascular function caused by digitalis are an outgrowth of this direct action of the glycoside on heart muscle fiber. Other actions of digitalis are secondary and not indispensable. This concept of digitalis action is supported by the overwhelming number of clinical and laboratory investigations and it is no longer necessary to seek extracardiac or vagal actions of digitalis to account for the benefit derived from the drug in heart failure.

For many years, digitalis was looked upon as influencing the heart mainly through the slowing of cardiac rate which occurred under certain circumstances. This was due to the fact that digitalis was thought to be specific in the treatment of auricular fibrillation, in which it often dramatically slows the ventricular rate.

The slowing in rate was believed to be the basis for relief of symptoms. In this manner, the primary action of digitalis on the heart muscle was minimized or ignored and the drug was not recommended for heart failure with normal rhythm but rather reserved for arrhythmias with rapid heart rate. Starting perhaps with Wenckebach in 1910 and continuing with the clinical observations of Pratt (1918), Christian (1919), Luten (1924), Marvin (1926) and many others, the conviction grew and finally became firmly established that digitalis was chiefly effective in congestive heart failure regardless of cardiac rhythm, and that it brought relief not by virtue of cardiac slowing but rather by its direct action to increase the force of the myocardial contraction.

Effect on the Force of Systolic Contraction. Digitalis acts on the myocardium to increase the force of systolic contraction. This has been demonstrated directly on strips of heart muscle, in isolated mammalian hearts, in heart-lung preparations, in experiments of various types in intact animals, and indirectly in man. As long ago as 1855, Vulpian, who was the first to experiment with digitalis, noted that it caused a systolic contracture of the frog's heart. This fundamental observation is still the basis of the U.S.P. bio-assay of digitalis on frogs. Accurate mammalian experimentation on the direct myocardial effects of the digitalis bodies was initiated by Cushny (1897) and countless investigators have contributed to the literature on this subject. Details must be sought in special reviews (Robinson, 1923; Cohn and Stewart, 1924; Cushny, 1925; Weese, 1936; Luten, 1936). To skip almost 90 years of investigation and cite examples of the modern type of work, the results obtained by Cattell and Gold (1938) on the isolated papillary muscle of the cat may be mentioned. They stimulated the muscle at a constant rate and employed concentrations of ouabain and digitoxin compatible with therapeutic amounts in man. The drugs increased the systolic tension several-fold whether the muscle was contracting at optimal or at high diastolic tensions (short diastolic length). These results appear to prove that digitalis acts directly on heart muscle to increase the force of systolic contraction independently of other cardiac or extracardiac factors. Working with tortoise hearts, Kabat and Visscher (1939) obtained results in essential agreement with those of Cattell and Gold. The primary action of digitalis glycoside (K-strophanthosid) was to cause an increase in the work capacity of the heart muscle without associated changes in diastolic elasticity of the ventricular muscle (cardiac tonus).

When digitalis increases the force of contraction in the failing heart, the ventricle empties more completely. The heart is rendered capable of caring for an increased venous return, and if venous pressure is high due to congestive failure, this pressure is lowered toward normal. The diastolic filling may be increased, especially if the rate of the heart is slowed. Not only is the force of systole improved but the length of time in each cardiac cycle occupied by systole is shortened. This naturally allows more time for the heart muscle to rest and for the ventricle to fill. Auricular muscle is also directly stimulated by digitalis, especially if circus movement is not present.

Not only does digitalis increase the force of contraction but it apparently increases the mechanical efficiency of heart muscle. Animal experiments indicate that after digitalis the heart is able to do a given amount of work with less consumption of oxygen (Gremels, 1933; Peters and Visscher, 1936). This may be related to the fact that digitalis decreases the diastolic size of the heart, and it has been shown that for a given amount of work the oxygen need of the heart increases as the diastolic size of the heart increases.

The strengthened cardiac systole caused by digitalis affects markedly other properties of the heart beat, and influences other aspects of cardiovascular function now to be considered.

Heart Rate. The present conception of the action of digitalis minimizes the importance of cardiac slowing as a factor in the beneficial effect of the glycoside in heart failure. The overemphasis placed on the slowing of cardiac rate after digitalis obscured for years not only the major and direct action of the drug on the myocardium but also the main indication for its use, namely, cardiac decompensation.

In animals, digitalis can be shown definitely to decrease the rate of the heart. This action is mediated in large part through the vagus nerves because it is not so manifest after atropinization or vagotomy, and it is not prominent in isolated hearts. The manner in which the vagus is stimulated by digitalis is not completely clear. Earlier explanations held that the glycoside excited the medullary vagal nuclei. Other work indicates that the drug sensitizes the pacemaker of the heart to the normal vagal impulses. Heymans and his coworkers (1932), from cross-circulation experiments in animals, concluded that perfusion of the vagal centers with digitalis does not slow the heart but that characteristic bradycardia results when the drug has access to the region of the carotid body. They therefore believe that the carotico-aortic vasoreceptor system is stimulated by digitalis (through hypertension) to cause *reflex* vagal slowing of heart rate. It may be noted that the clinical investigations of Weiss and coworkers (1938) indicate that digitalis increases the excitability of the carotid sinus and enhances the tendency to arrhythmias and cardiac arrest in patients with hyperactive carotid sinus reflexes. *The most likely manner in which digitalis causes vagal slowing of the rapid heart rates seen in clinical heart failure is reflexly through restoration of cardiac compensation.*

Regardless of the fact that bradycardia occurs after digitalis in animals, *the question of importance is whether the therapeutic effects of digitalis in man are the result of digitalis-induced vagal slowing.* Congestive heart failure is often relieved in man by clinical doses of digitalis without evidence of cardiac slowing. Furthermore, if slowing does occur, benefit may be observed earlier than any change in rate. Again, when the rate is decreased by digitalis it is mainly in patients who have a tachycardia accompanying the heart failure. Even in auricular fibrillation where digitalis exerts its most prominent slowing of ventricular rate, the drug usually does not slow the ventricle unless heart failure exists. One must therefore conclude from these basic clinical observations that *digitalis may cause conspicuous improvement in heart failure without the intervention of primary cardiac slowing.* This conclusion is strengthened by the fact that changes in heart rate are insignificant and variable when full doses of digitalis are given to persons without cardiac failure.

The foregoing discussion is not intended to signify that slowing does not occur after digitalis but only that it is not a necessary or primary factor in the relief obtained. The mechanism of the decrease in ventricular rate by digitalis in patients with auricular fibrillation will be discussed later. In cases of failure with a sinus tachycardia, the glycoside also slows the heart rate. The inference cannot be drawn that the drug acts directly on the sinus mechanism to slow the rate. Tachycardia in heart failure is usually considered a compensatory response to maintain the circulation. As digitalis improves the circulation and relieves the failure by its myocardial action, the cause of the tachycardia is corrected and the heart rate is decreased. The normal factors adjusting and controlling heart rate are involved in this slowing which is largely reflex in nature. Slowing, therefore, results from reflex increase to normal in vagus tone and a corresponding decrease in cardiac sympathetic discharge.

It is fortunate that the quieting effect of digitalis on the rapid rate of failing hearts is accomplished through the basic mechanism of improved muscular ability of the heart (Luten, 1936). If the slowing produced by digitalis were a primary effect unrelated to the restoration of cardiac compensation, the result might be much less salutary. As Wiggers (1931) has aptly pointed out, "There is no medicinal agent by which a compensatory sinus tachycardia can easily be abolished; otherwise many a patient with serious heart disease would have been helped prematurely to his grave through kindly intentioned but misguided treatment."

Toxic doses of digitalis rather characteristically cause excessive slowing of the heart rate. This is due in part to a vagal effect but in larger part to a direct action of the glycoside on the pacemaker and conduction tissue. The details of this toxic type of slowing are presented in the section on digitalis poisoning.

Special Aspects of Digitalis Action on the Heart Rate. (1) *Effect on the Cardiac Pacemaker.* In patients with heart disease and normal sinus rhythm, digitalis in therapeutic amounts produces neither constant nor significant slowing of the heart rate. This is true whether the heart is compensated or in failure. In normal healthy individuals, full doses of the glycoside may cause some slowing of rate but this averages only about eight beats per minute. Therefore if therapeutic amounts of digitalis affect the sinoauricular node of man directly or through vagal stimulation, this action is not prominent. Even in patients with sinus tachycardia due to hyperthyroidism or infection, digitalis in full doses has little restraining action on the rate of pacemaker discharge. Toxic doses of digitalis, however, affect the sinoauricular node directly.

(2) *Effect on the Conduction System.* Conduction between the auricle and ventricle is slowed by clinical doses of digitalis and this may be reflected in an increased P-R interval in the electrocardiogram. The slowing of conduction occurs in normal as well as in decompensated hearts. The action of digitalis on conduction is partly vagal in origin but mainly a direct action of the drug on the conduction bundle. It must not be forgotten that the bundle of His is composed of muscle tissue which shares the same cardiotonic effect of digitalis as does the remainder of the myocardium. When cardiac muscle contracts more strongly, its refractory period is increased and its rate of conduction is decreased. Under certain circumstances, both these factors tend to impede auricular impulses from reaching the ventricle. When a normal sinus rhythm exists and the auricular impulses are neither numerous nor weak, they can all get through to excite the ventricle even though clinical doses of digitalis have somewhat delayed their passage. The A-V delay in itself, therefore, under these circumstances does not cause any change in cardiac rate. With toxic amounts of digitalis, however, degrees of A-V block may occur which so interfere with the transmission of auricular impulses that partial heart block or complete auriculoventricular dissociation may result.

(3) *Mechanism of Cardiac Slowing in Auricular Fibrillation.* Although therapeutic amounts of digitalis do not materially slow the rate of the heart with a normal sinus rhythm, the same dose of drug may have a pronounced effect on the ventricular rate in patients with auricular fibrillation. In this arrhythmia, the auricular impulses are quite weak and may number well over 500 per minute. A large number of these impulses are automatically blocked by the conduction system and never reach the ventricle because the A-V bundle cannot normally conduct more than 270 impulses per minute. Others arrive during the refractory

phase of the ventricle and consequently are ineffective. Nevertheless, altogether too many auricular impulses manage to reach the ventricle which thus beats rapidly and irregularly. When digitalis is given in full doses to patients with auricular fibrillation, the ventricular rate is often reduced to an optimal level (Figure 50). Both the vagal factor in slowing and the direct actions of digitalis on the conduction system cooperate to block auricular impulses (Gold and coworkers, 1939). As already stated, digitalis acts directly on the A-V conduction system to increase the refractory period and slow the rate of conduction. In addition, reflex vagal stimulation caused by digitalis affects the bundle of His to weaken impulse conduction. As a result, the number of impulses capable of passing over the bundle of His per minute is reduced appreciably. That the vagal component of the A-V depression is not indispensable is evident from the fact

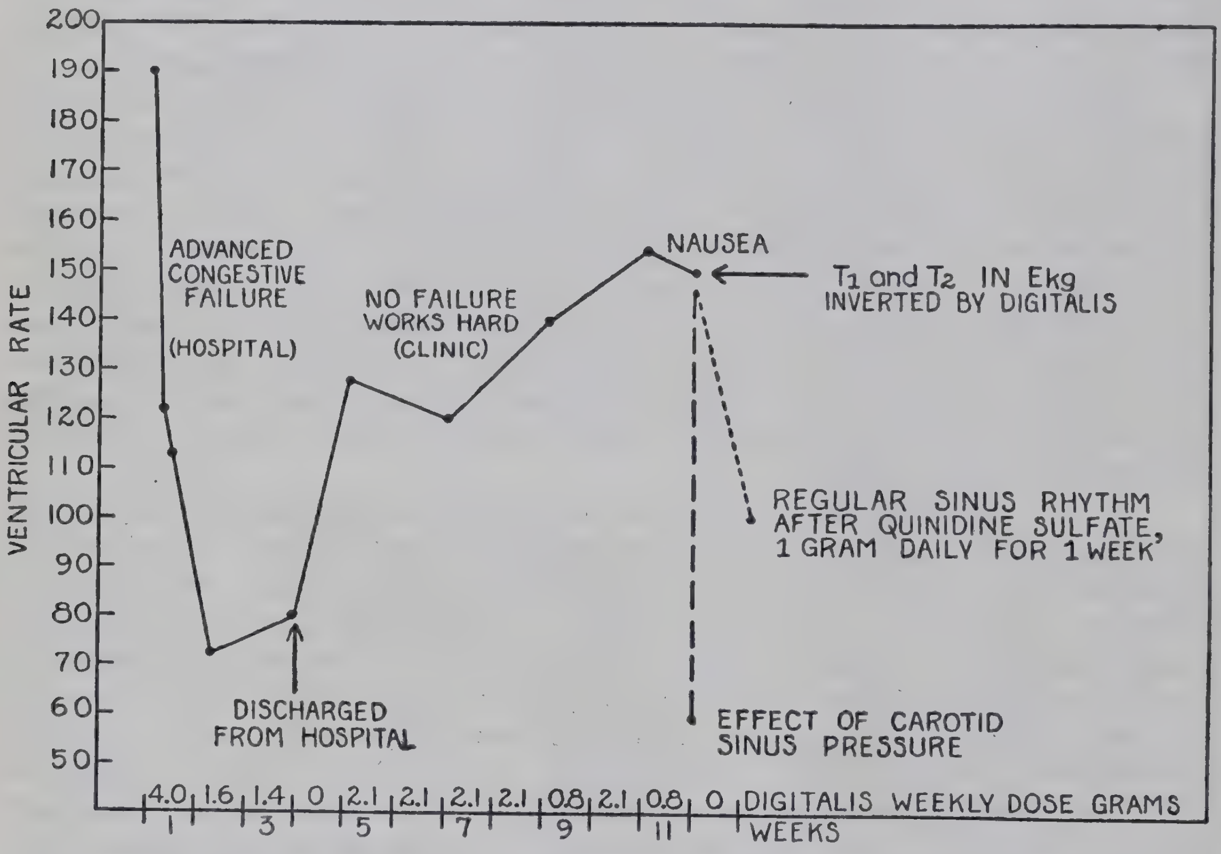


FIGURE 47. *Effect of digitalis on the tachycardia of heart failure and hyperthyroidism as compared with that of hyperthyroidism alone.*

Female, aged 52, weight 144 pounds. Diagnosis: Congestive heart failure and auricular fibrillation, on the basis of hyperthyroidism. The weekly dose of digitalis is indicated in grams along the abscissa and the ventricular rate on the ordinate. While confined in the hospital with advanced congestive cardiac failure requiring emergency measures (phlebotomy, oxygen), the patient responded to digitalis and rest in bed with a slowing of ventricular rate to 70. After discharge from the hospital, while working hard and manifesting no physical signs or symptoms of congestive failure, the patient's ventricular rate gradually increased due to the thyrotoxicosis. Tachycardia persisted in spite of adequate doses of digitalis.

It is clear that digitalis slowed the rapid ventricular rate in this case only when failure was present, by restoring a competent circulation through improved myocardial function. When failure was absent, digitalis had no effect on the tachycardia. That the heart would have been able to respond with slowing if digitalis had any primary and direct action on the vagus mechanism is indicated by the fact that carotid sinus pressure produced reflex vagal slowing from 150 down to 60 beats per minute, a degree of slowing unusual in patients with auricular fibrillation. Thus digitalis-induced slowing in patients with tachycardia due to heart failure is secondary to restoration of cardiac compensation. (After Gold, Kwit, Otto and Fox, 1939. Courtesy of the *Journal of Pharmacology and Experimental Therapeutics.*)

that slowing may still occur after full doses of atropine or after vagotomy. The importance of the increase in refractory phase of the junctional tissue itself as the mechanism by which digitalis slows the ventricle in auricular fibrillation is too often overlooked.

Gold and associates (1939) have analyzed the relative importance of the vagal and extravagal components of the digitalis-induced slowing of the ventricular rate in patients with auricular fibrillation. The slowing produced by small doses of digitalis could largely be attributed to vagal stimulation in that the cardiac rate could be increased by large doses of atropine. This vagal slowing was interpreted as being largely reflex in nature and due to restoration of myocardial compensation. After full doses of digitalis, however, atropine no longer was capable of increasing cardiac rate and the ventricular slowing was clearly due to extravagal actions of digitalis (Figure 47).

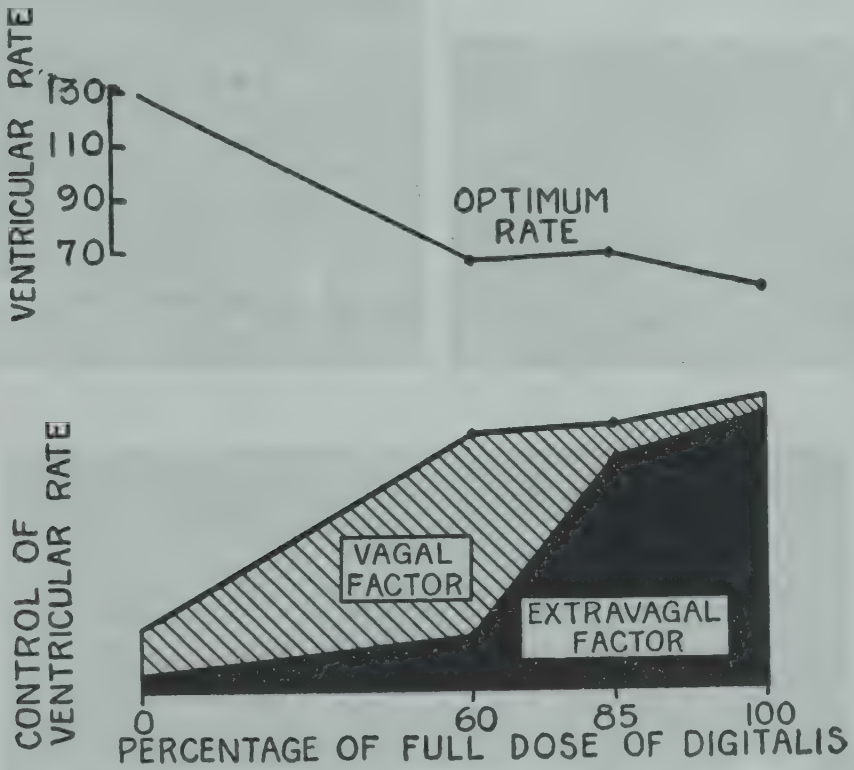


FIGURE 48. *Schematic representation of the mechanism by which digitalis slows the ventricular rate in patients with auricular fibrillation and congestive heart failure.*

The ventricular rate is shown in the upper portion of the figure, and the relative rôles in the cardiac slowing played by vagal and extravagal factors as the dose of digitalis is increased are indicated in the lower shaded and solid black sections, respectively. As small suboptimal doses of digitalis improve myocardial function, there is a resulting increase in the reflex activity of the vagus (vagal factor). Consequently, the ventricular rate is slowed. Atropine is effective in counteracting the reflex vagal activity and thus speeds the heart at this stage of digitalization. As the dose of digitalis is increased, the rate falls further and the direct action of the drug on the conduction system, *i.e.*, the extravagal factor, becomes more prominent. As the optimal rate is reached, the extravagal factor plays an increasingly dominant part in the control of the ventricular rate. Atropine does not annul the slowing due to the direct action of digitalis on conduction in heart muscle. Through a certain range, the ventricular rate remains constant and optimal despite the increasing depression of conduction caused by increasing amounts of digitalis. It is important to recognize that even though the ventricle is optimally slowed, one cannot predict from the degree of slowing exactly which mechanism, the vagal or extravagal, is dominant. The dominance of the extravagal factor is much to be desired as the more favorable for maintaining the optimum cardiac state in patients with auricular fibrillation and heart failure. (After Gold, Kwit, Otto and Fox, 1939. Courtesy of the *Journal of Pharmacology and Experimental Therapeutics.*)

Certain clinical observations make it appear that too much significance should not be attached to the digitalis effects on the junctional tissue as the mechanism by which digitalis slows the rate in clinical auricular fibrillation. In some cases of this arrhythmia, ventricular slowing may not occur at all after usual doses of digitalis. Evidently the factor deciding whether digitalis will decrease the ventricular rate in auricular fibrillation is the presence or absence of heart failure (Luten, 1936; Luten and Jeffreys, 1936). The direct action of digitalis on the decompensated myocardium is to strengthen the force of its contraction which automatically increases the refractory period of the muscle. The ventricle is thus rendered less excitable to the auricular impulses which manage to get through the junctional tissue from the auricle. Probably more important is the fact that the irritability of the myocardium is further reduced by the restoration of an adequate

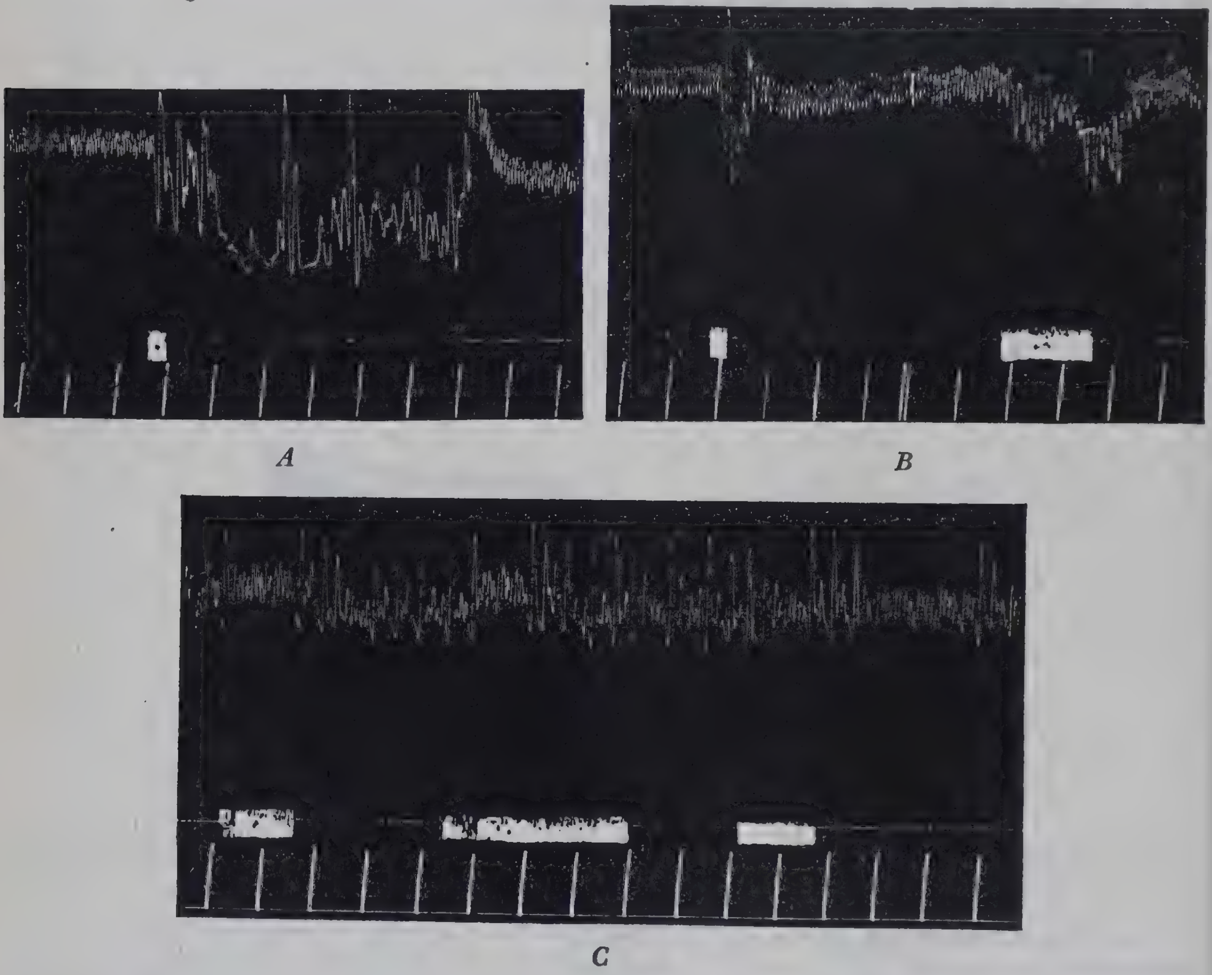


Figure 49. *The action of large doses of digitalis on auriculoventricular conduction in experimental auricular fibrillation.*

Dog, morphine-chloretone anesthesia, heart exposed, artificial respiration. Top line, carotid blood pressure; middle line, stimulation signal; bottom line, time in five second intervals. The auricles are periodically caused to fibrillate by means of an electric current delivered through Hirschfelder electrodes fastened to the auricle. The strength of the stimulus is not varied. *A.* Before digitalis, the effect of a short period of auricular fibrillation on the blood pressure and the rhythm of the ventricle. *B.* After 15 intravenous doses of digitalis, each corresponding to 0.25 cc of tincture of digitalis. *C.* After 27 doses. Note that the ventricle becomes less and less susceptible to the numerous auricular impulses arriving during the periods of fibrillation. At *C,* the ventricle is beating independently of the auricle (complete A-V dissociation) and a ventricular extrasystolic rhythm is present, caused by the very large doses of digitalis employed. The apparently slow ventricular rate appearing in *A* and *B* during periods of auricular fibrillation is due to a recording artefact resulting from the inertia of the mercury manometer. (After Barbour, 1932. Courtesy of Lea and Febiger.)

circulation and hence by an improvement in the coronary blood flow and nourishment of the heart muscle. A partially anoxic heart is known to be more irritable and hence will respond to stimuli which ordinarily are incapable of exciting it to contract. The tachycardia observed in many cases of auricular fibrillation with failure thus appears to be due to the failure itself. Tachycardia of an equal extent in auricular fibrillation not accompanied by failure, and due to a toxin increasing ventricular irritability, is not slowed by digitalis.

In *summary,* therefore it may be stated that ventricular slowing produced by digitalis in auricular fibrillation is the result of a dual mechanism. The more important is operative when heart failure is present in which case the drug restores compensation by improved ventricular power and thereby reduces the hyperexcitability of the ventricle to auricular impulses. Coincidentally, the vagal factor in the control of heart rate is restored. The second factor in slowing is the depressant action of digitalis on the conduction of auricular impulses through the junctional tissue. This latter factor appears to be secondary unless failure is absent or large doses of digitalis are employed (Figure 49).

In *auricular flutter,* digitalis acts similarly, but the effect of the glycoside on the junctional tissue is often intentionally sought by administering doses bordering on the toxic. In this arrhythmia, A-V block already exists and if this can be increased the ventricular rate falls appreciably. For example, if a 2:1 block is changed by digitalis to a 3:1 block, the ventricular rate is decreased by one-third. The direct action of large amounts of digitalis on the circus movement of the auricular muscle is also desired in this disorder, as explained later.

(4) *Slowing of the Heart Rate in Children.* It has been claimed that in children the vagus mechanism is especially susceptible to the action of digitalis and that cardiac slowing is therefore more important in the salutary effects of the glycoside in children than in adults. It appears, however, that no such special sensitivity exists. The misconception has arisen from the use of toxic amounts of digitalis in an attempt to obtain results, because the type of heart failure occurring in children is often refractory to digitalis. This refractoriness is probably explained by the fact that heart failure in children is usually due to an active carditis. Therapeutic benefit from the drug depends upon a direct cardiotonic action in children as well as in adults, and when improvement occurs it appears before and often without cardiac slowing.

Heart Size. Full doses of digitalis decrease the diastolic size of the heart. This is thought to be true for normal human hearts as well as those which are dilated in failure (Figure 50). Careful study of the surface area of the hearts of normal and decompensated individuals, as recorded by teleoroentgenograms, reveals a substantial decrease in heart size (Stewart and Cohn, 1932). In animals, both the normal heart and the heart with experimentally produced dilatation can be shown to decrease in diastolic size when full doses of digitalis are given (Cohn and Stewart, 1928).

The effect of digitalis on the diastolic size of the heart is undoubtedly related to the direct action of the drug on heart muscle. The finer mechanism of this alteration in diastolic volume, however, is disputed. There is much controversial literature on the question whether heart muscle has "diastolic tone." It is not known whether the myocardial fibers, during diastole, possess a degree of slight contraction (tonus) which offers resistance to the blood flowing into the ventricles and thus controls the degree to which the chambers fill. (See Johnson and Katz, 1937; Fishberg, 1938, and Best and Taylor, 1939, for discussions concerning tone in cardiac muscle.) The expression "diastolic tone," however, has come to be used rather loosely to signify diastolic size of the heart rather than myocardial tonus during diastole, as would be required in strict physiological parlance. For example, the decreased diastolic size of the heart occurring after digitalis is often considered to represent an increase in "diastolic tone." A decrease in diastolic volume, however, could also be due to a diminished venous return, a shortened duration of diastole, etc., quite independently of cardiac tonus. Indeed, Gold and Cattell (1938, 1939, 1940) and Kabat and Visscher (1939) hold that digitalis bodies are effective in heart failure not by increasing cardiac tone, as claimed by Stewart and Cohn and their associates, but by improving the strength of systolic contraction through a direct action on the myocardium. The experiments on papillary muscles and tortoise hearts referred to previously (page 505) indicate that digitalis enhances the force of systole without a decrease in diastolic length and throughout a wide range of diastolic lengths. It must be remembered, however, that the comparatively simple conditions existing in the experiments described cannot duplicate all the complex interrelated circulatory factors of the failing human heart in clinical cardiac decompensation. It is not profitable here further to pursue the question whether the decrease in diastolic length of the heart fibers (increase in "tone") is a primary action of digitalis or whether the increased systolic force of contraction alone can account for all the effects observed. The interested reader is referred to the critical review by Gold and Cattell (1940).

The important effects, especially on cardiac output and venous return, of the increased force of ventricular contraction and the decrease in diastolic heart size (increased "tone") may now be considered.

Cardiac Output. Many closely interrelated factors combine to determine cardiac output. These include heart rate, heart size, stroke volume, velocity of blood flow, peripheral resistance and venous return. The interpretation of the action of digitalis on cardiac output is therefore not a simple matter. In human beings or animals with normal hearts, cardiac output is definitely diminished by digitalis (Figure 50). In man, the decrease ranges between 20 and 35 per cent. This is due to the fact that the heart is decreased below its optimal size by the direct cardiotonic action of the drug. The capacity of the ventricular chamber is reduced and hence the stroke volume is lessened (Cohn and Stewart, 1928; Stewart and Cohn, 1932).

The fact that cardiac output in normal hearts is unfavorably influenced by digitalis led some workers to the conclusion that the drug was contraindicated in heart failure with normal rhythm. In failing hearts, however, cardiac output is not diminished by digitalis but is increased. This is demonstrable in man, intact animals or heart-lung preparations. As is the case in the normal heart, cardiac size is reduced but this change is from a dilated inefficient ventricle toward a more normal and efficient one. As a result of a more optimal diastolic size, stroke volume is increased, and systolic ejection of blood is more forceful and complete. The output increases regardless of the rhythm and independent of cardiac rate (Figure 50). It must be emphasized that the basic mechanism of digitalis action is the same in health and disease, namely to decrease the size of the ventricular chamber and increase the force of the ventricular contraction. The effect on cardiac output, however, depends on whether the chamber is originally normal or dilated. This interpretation has been advanced especially by Stewart and Cohn (1932).

The clinical studies of Stewart and collaborators (1938) have confirmed and advanced the aforementioned concepts of the effect of digitalis on cardiac output.

In 20 patients with congestive heart failure, showing decreased cardiac output and increased heart size, with normal rhythm or auricular fibrillation, digitalis caused the following changes: the cardiac output per minute and per beat was enhanced; the heart size was diminished; venous pressure fell if it was elevated; the velocity of blood flow was more rapid; and the work of the left ventricle per beat was increased and became more closely commensurate with heart size than before digitalis (Figure 50). The effects following digitalis in 22 patients with

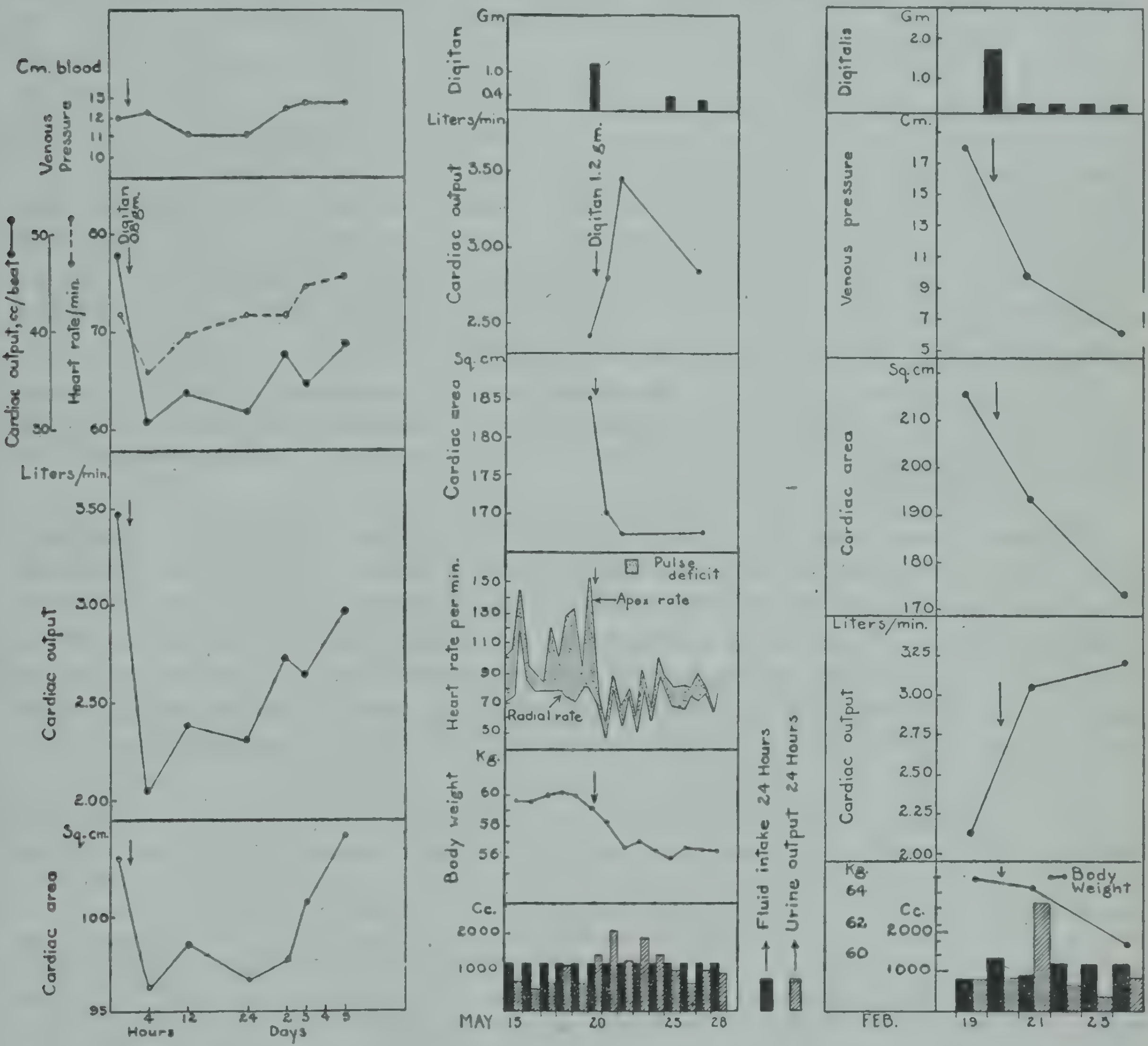


FIGURE 50. *The effect of digitalis in normal individuals and in patients with congestive heart failure.*

Left: Normal woman, aged 33, weight 52.5 kg. Digitan, 0.8 gram, decreased the cardiac area and this was accompanied by a fall in cardiac output per beat and per minute. The venous pressure and heart rate were not significantly altered. The slow return to normal of the cardiac area was associated with an increase in cardiac output.

Center: Woman, aged 51, congestive heart failure (fourth attack), auricular fibrillation, premature ventricular contractions, pulse deficit and edema. Digitan, 1.2 grams, produced diuresis, decrease in body weight, diminution in pulse deficit and ventricular rate, and a decrease in cardiac area accompanied by an increase in cardiac output. Effects were maximal within 48 hours.

Right: Man, aged 32, rheumatic heart disease, congestive heart failure, normal sinus mechanism. Digitalis, 1.7 grams produced diuresis, fall in body weight, return of elevated venous pressure to normal, and a decrease in cardiac area associated with an increased cardiac output.

Contrast the effects of digitalis on the cardiac size and output of the normal and decompensated heart. (After Stewart and Cohn, 1932, and Stewart, Deitrick, Crane and Wheeler, 1938. Courtesy of the *Journal of Clinical Investigation* and the *Archives of Internal Medicine*.)

compensated organic heart disease (no congestive failure) and with normal rhythm or auricular fibrillation were quite variable and unpredictable. Some of the patients responded like those with normal hearts, that is, showed a decrease in heart size and diminished cardiac output. Other patients reacted like those with congestive heart failure, that is, showed a decrease in heart size and an increase in cardiac output. Still other patients showed no alteration in heart size or cardiac output. In all instances, however, a decrease in cardiac output was always associated with a decrease in heart size; conversely, where the output was not affected, cardiac size was not altered. The conclusion drawn by Stewart and associates is that digitalis decreases heart size in heart failure and thus increases cardiac output. It does this by making the heart more efficient as a pump both in respect to its size and to the strength of contraction. Also, digitalis increases the work accomplished by the heart per beat, regardless of the ultimate effect on cardiac output, and regardless of the preexisting rhythm. The work of the heart thus becomes more nearly appropriate for the size of the organ. It is evident that Stewart and Cohn and their associates place more stress on the effect of digitalis to increase heart "tone" in contrast to the view of Gold and Cattell who emphasize the effect to increase the force of systolic contraction.

Evidence exists that digitalis produces an *increase in circulatory velocity* in patients with heart failure. This also strongly suggests that stroke volume is increased, because the rate of blood flow is enhanced independently of a change in cardiac rate or in the caliber of the peripheral vascular bed.

Venous Pressure. In the presence of increased venous pressure due to congestive heart failure, digitalis decreases the venous pressure. A fall of pressure from 20 cm of water to five cm within 24 hours is not unusual (Figure 50). This decrease in venous congestion is undoubtedly secondary to the improvement which occurs in the circulation and especially to the increased cardiac output. In normal patients or in those with isolated left ventricular failure, the systemic venous pressure is not elevated and digitalis has no significant effect on it (Figure 50).

Some competent workers, however, maintain that the primary action of digitalis is to lower the venous pressure and by this means remove the venous congestion of the failing heart and allow it to recover its efficiency. Evidence in support of this interpretation has been obtained especially in experiments on the dog (Dock and Tainter, 1930; Katz and collaborators, 1938). It is claimed that the site of action of therapeutic doses is on the peripheral vessels, in particular on those of the liver. Digitalis is said to constrict the smooth muscle in the hepatic vein, pool the blood in the liver and portal system, relieve the right side of the heart of the overdistention imposed by venous congestion, and in this manner improve cardiac function. Only toxic doses of the glycoside are admitted to be capable of action directly on the heart, and then only deleteriously so far as cardiac output and efficiency are concerned. Indeed, Katz and coworkers (1938), from experiments on the isolated dog's heart, claim that digitalis has no direct effect on the contractile power or mechanical efficiency of the myocardium either in the "physiological" or failing state. Supporters of the peripheral vascular site of action of digitalis believe that the drug acts favorably in congestive heart failure by storing blood in the splanchnic area, thus reducing circulating blood volume and venous pressure, that is, by performing a "bloodless venesection." This view stresses the importance of venous pressure in heart failure and assumes that digitalis acts on the hepatic veins of man as it does in the dog.

There are, however, many observations against this interpretation. First, according to most observers, heart failure is the cause rather than the result of increased venous pressure. Secondly, the venous pressure in marked congestive failure is insufficient to be a factor in stretching of the right ventricle. Thirdly, in isolated left ventricular failure, digitalis causes restoration of compensation without significant change in venous pressure. Fourthly, digitalis causes a decrease in the size of the swollen liver in congestive failure rather than an increase which is necessitated by the above theory. Finally, the amount of smooth muscle in the hepatic veins of man is quite sparse and forms no distinct sphincter for a sluice mechanism as does the more abundant smooth muscle in the dog. A critical analysis of the "liver" hypothesis of the action of digitalis has been presented by Gold and Cattell (1940).

Circulatory Volume. For reasons not fully understood, congestive heart failure is accompanied by an increase in the circulating blood volume (Fishberg, 1938). Digitalis acts to decrease the blood volume and probably does so by restoring cardiac compensation and removing the causes underlying the original increase. In patients with normal hearts, however, digitalis may also cause a diminution in circulatory blood volume. The mechanism of this action awaits elucidation.

Blood Pressure. In animals, digitalis may produce a rise in blood pressure due especially to a direct action on the smooth muscle of blood vessels but also in part to central vasomotor stimulation. Amounts required to cause this rise are toxic and out of all proportion to those used in man. Doses in animals comparable to those used clinically exert no such vascular constriction. Therapeutic amounts of digitalis cause no constant or significant change in the blood pressure of normal human beings.

In patients with heart failure, the administration of digitalis causes variable changes in blood pressure. The pulse pressure may be increased due to a lowering of diastolic pressure. This lowering may be the result of a reduction of vasomotor tone, elevated by a relative anoxia. The systolic pressure may also fall somewhat, especially if its level was high as a result of overcompensation subsequent to the failure. Low systolic pressures due to decompensation are elevated toward normal as digitalis improves cardiac function. It is clear, therefore, that digitalis affects blood pressure only through its action on the heart and not by any significant effect on the blood vessels or vasomotor center. The former hesitancy regarding the use of digitalis in hypertensive patients has no basis in fact. Patients who have hypertension and isolated left ventricular failure are often greatly benefited by the glycoside.

Comparison of Responses to Digitalis in Health and Disease. The salient features of the foregoing discussion are summarized in Table 30 and in Figure 50 which compare the actions of full doses of digitalis in patients with normal hearts and in those with congestive heart failure.

TABLE 30

RESPONSES TO DIGITALIS IN HEALTH AND DISEASE

EFFECTS OF DIGITALIS ON	PATIENTS WITH NORMAL HEARTS	PATIENTS WITH HEART FAILURE
Ventricular rate	Slight decrease as a rule	Usually decreased if previously rapid
Blood pressure	No significant change	No uniform or marked effect. May be increased if low, decreased if high
Venous pressure	No significant change	Decreased if elevated
Cardiac size	Decreased below normal	Decreased toward normal
Cardiac minute volume output	Decreased	Increased
Velocity of blood flow	Increased or decreased	Increased as a rule
Circulating blood volume	Diminished (?)	Diminished
Symptoms	May experience lassitude, dyspnea, substernal pain, etc.	Relief of dyspnea, cyanosis, edema, ascites, etc.

Coronary Circulation. Divergent views exist as to the effect of digitalis on the coronary blood flow. Some workers believe that the coronary vessels are an exception to the statement that toxic doses are necessary to cause vascular constriction, and they report coronary vasoconstriction from therapeutic amounts (Gilbert and Fenn, 1932). This view has its supporters in the clinical field who contend that digitalis in patients with angina pectoris tends to increase the incidence of attacks of pain. The opinion has therefore gained ground in some quarters that digitalis is contraindicated in angina pectoris.

That the digitalis glycosides in experimental animals decrease coronary blood flow is by no means agreed upon and some investigators have found an increase after the drug (Bodo, 1928; Hochrein, 1932; Rein, 1933; Ginsberg, Stoland and Siler, 1938). Essex, Herrick and Visscher (1938) reexamined this question by using the thermostromuhr method to test the mean blood flow through the circumflex branch of the left coronary artery in trained intact dogs. They found that full subnauseating doses of the native glycosides of digitalis lanata (digilanids A, B and C) have no effect on coronary blood flow.

The occurrence of pain in digitalized patients with angina pectoris cannot be accepted as presumptive evidence either that digitalis was the cause of the pain or that the drug induced pain by producing coronary vasoconstriction. In a careful and extensive study of 120 selected patients with angina pectoris without decompensation, Gold and coworkers (1938) demonstrated that digitalis does not increase or decrease the incidence of anginal attacks and that even large doses rarely, if ever, produce effective constriction of the coronary arteries. It must be concluded, therefore, that clinical doses of digitalis have not been shown to affect deleteriously the coronary circulation in man. Indeed, the blood supply to the failing myocardium may be improved as a result of the restoration by digitalis of cardiac compensation.

Diuretic Action. Withering employed digitalis in cardiac dropsy and for many years the foxglove was considered a diuretic. In no sense, however, is digitalis a true diuretic and its effects on urine flow are manifested entirely through its action on the heart and the circulation. In normal persons or in patients with heart failure but without edema or serous effusions, no diuresis is noted after digitalis. In cases with anasarca due to causes other than congestive heart failure, the glycoside likewise causes no increase in urine output. Furthermore, when digitalis fails to restore cardiac compensation in patients with cardiac edema, diuresis fails to develop. It is thus irrational to expect the drug to improve renal function which is unimpaired by a faulty circulation or to remove accumulations of fluid not due to heart failure.

It is clear, therefore, that diuresis following digitalis is secondary to the relief of heart failure. The mobilization of edema fluid causes the diuresis and not vice versa. Experiments on heart-lung-kidney preparations designed to demonstrate a direct action of cardiac glycosides on renal tubular cells to inhibit water reabsorption and thus cause diuresis do not duplicate clinical conditions, and results obtained from such experiments cannot be accepted as evidence for an extracardiac diuretic action of digitalis.

Diuresis is often one of the first prominent manifestations of digitalis action in edematous patients with congestive heart failure (Figure 50). Urinary output may rise within 24 hours from 200 cc per day to three liters or more. The specific gravity of the urine falls, the concentration of chlorides increases, the albuminuria diminishes and the phenolsulphonphthalein output rises. The body weight falls even when the edema is occult, and reveals the diuretic response to the improvement in heart function.

The main cause of edema and serous effusion in congestive heart failure is the increase in hydrostatic pressure in the venous ends of capillaries, preventing the normal resorption of extracellular fluid. This is discussed in detail elsewhere (page 643). As heart failure is relieved and venous congestion reduced, the edema fluid is returned to the blood. The resulting hydremia can actually be detected by a fall in the specific gravity of the plasma which occurs before diuresis is evident, affording additional proof that mobilization of edema fluid is the cause and not the result of the diuresis. Renal function is also improved by the relief of vascular congestion in the kidney. The better appetite and improved gastro-intestinal absorption resulting from a return of cardiac compensation lead to an increase in the concentration of serum protein, which may be sufficiently low in congestive heart failure to contribute to the edema formation. Fluid shifts similar to those occurring in the tissues and systemic circulation, as a result of failure of the right ventricle, also take place in the lungs and pulmonary circulation as a result of insufficiency of the left ventricle. Thus, when digitalis improves the function of the left side of the heart, pulmonary venous pressure is lowered and the signs and symptoms of pulmonary edema, such as râles and dyspnea, disappear.

Despite the effect of digitalis in mobilizing edema fluid in congestive heart failure, roughly one-half of all patients require additional and specific measures to promote diuresis (Figures 68 and 70). These are discussed in the chapter on diuretics.

Electrocardiographic Effects. Digitalis produces characteristic electrocardiographic changes which are often important in determining whether a patient has been receiving digitalis within the previous two or three weeks. However, these changes cannot in themselves be used for the purpose of quantitatively estimating digitalis dosage. Furthermore, the effects of digitalis are often superimposed on the changes resulting from the basic cardiac disease. The electrocardiogram must be interpreted with this fact in mind.

Within two to four hours after large oral doses of digitalis, definite alterations may appear in the electrocardiogram. This illustrates that the drug can be depended upon to act quickly when given by mouth. The first changes are noted in the RS-T segment or in the T wave itself. The normally upright T wave may become diminished in amplitude, flat or inverted in one or more leads. The RS-T interval may also show depression (Figure 51). Either of these changes may occur alone or both may coincide. Digitalis may result in a depressed T wave in lead I with an elevated T wave in lead III or vice versa, especially in cases where

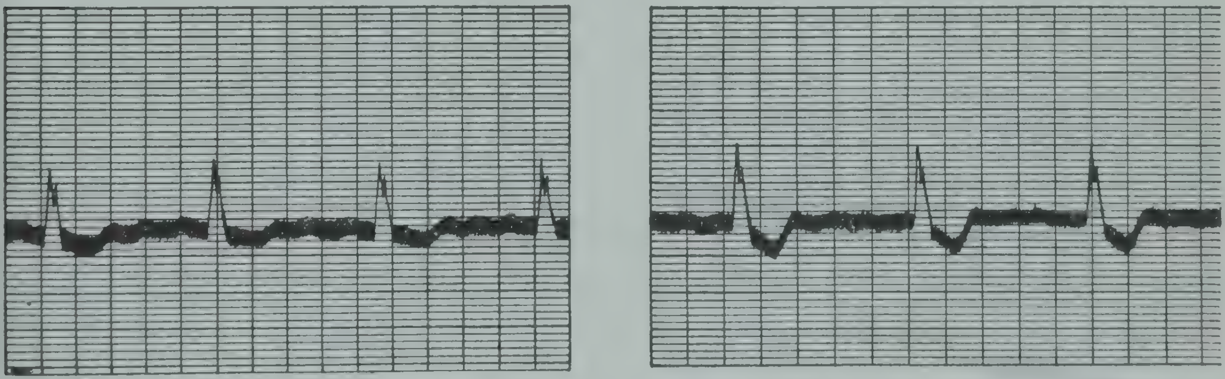


FIGURE 51. *Effect of digitalis on the RS-T segment and P-R interval.*

Female, aged 68, hypertensive arteriosclerotic heart disease. ECG: Lead 2. *Left:* P-R interval, 0.20 second. Early digitalis effect is seen in the sloping depression of the RS-T segment. *Right:* Tracing taken several days later shows considerably deeper depression of the RS-T segments in a manner typical of digitalis, and a marked increase in the P-R intervals to 0.30 second (incomplete A-V block). (Courtesy of Dr. A. J. Geiger, Yale University School of Medicine.)

there is a marked axis deviation with the T waves opposite in direction to that of the predominant portion of the Q-R-S complex. The T wave alterations may occasionally resemble those seen after coronary occlusion. This is particularly true in chest leads. Indeed, the alterations caused by digitalis in the form of the T waves and RS-T segments of the chest lead may simulate those resulting from coronary artery disease or recent coronary occlusion, and may cause confusion in the interpretation of the record if it is not known that the glycoside has been administered (Stewart and Watson, 1938). The changes in the RS-T interval and T wave are due to a direct action of digitalis on the heart muscle and are not affected or abolished by atropine.

The P-R interval may be prolonged by digitalis (Figure 51). This effect occurs somewhat later than those described above. The interval is rarely greater than 0.25 second. If it is greater than this after digitalis, preexisting disease of the conduction system may be assumed, and the degree of myocardial damage that this signifies is sufficiently great to reduce definitely the possibility of a good response to the drug. Atropine will abolish the lower grades of A-V block produced by digitalis signifying that they are in good measure due to the vagal effects of digitalis. Higher grades of block are not significantly affected by atropine and are due to a direct action of the glycoside on the conduction bundle.

The Q-T portion of the tracing is shortened by digitalis and reflects the fact that the drug lessens the duration of ventricular systole. Large doses may occasionally cause changes in the size and shape of the P wave and result in abnormal rhythms which are detectable in the electrocardiogram. Almost every type of tracing due to cardiac disorders, except intraventricular conduction defects, can be simulated by the effects of digitalis on the heart.

That the T wave changes usually occur before the P-R interval is prolonged indicates again that digitalis acts first and foremost on the heart muscle itself. The T wave alterations may require two to three weeks or longer to disappear after the drug is stopped. Experiments on cats illustrate the order of appearance of the electrocardiographic changes in relation to the percentage of the lethal intravenous dose of digitalis required to elicit them, as follows (Robinson and Wilson, 1918): T wave effects appear after 24 per cent of the lethal dose; P-R interval increased after 53 per cent; ectopic beats after 72 per cent; complete A-V dissociation after 80 per cent.

Symptoms and Signs of Digitalis Overdosage. The toxic effects of digitalis are largely extensions of the therapeutic actions of the drug. For this reason, a "nontoxic" digitalis does not exist. A preparation which will not cause digitalis poisoning when given in excess is also one which will not exert any therapeutic effect. This point is an important one to recall when the physician is appraising the claims made by pharmaceutical firms for their particular brands of digitalis, its purified fractions or substitutes. The use of digitalis carries with it the obligation to understand and recognize those toxic actions of the drug which call for cessation of therapy. Only in this way can successful results be obtained with digitalis.

Withering wrote, "The foxglove when given in very large and quickly repeated doses, occasions sickness, vomiting, purging, giddiness, confused vision, objects appearing green or yellow; increased secretion of urine, with frequent motions to part with it; slow pulse, even as low as 35 in a minute, cold sweats, convulsions, syncope, death. . . . I am doubtful whether it does not sometimes excite a copious flow of saliva."

This discerning description applied to the effects of large acute doses because

Withering was unacquainted with the prolonged use of maintenance amounts of foxglove. Digitalis poisoning, as usually encountered today, is due to the continued ingestion of the drug in amounts greater than are destroyed or eliminated. The glycoside accumulates in the body and perhaps especially in heart muscle.

Gastro-intestinal Effects. Anorexia, nausea and *vomiting* are among the earliest evidences of digitalis overdosage. The emetic effects of the cardiac glycosides were known for centuries, and squill in particular was used as an emetic. Withering recognized that vomiting did not occur immediately upon taking foxglove and that this was an untoward side-action of the drug.

Anorexia usually occurs a day or more before nausea and vomiting develop. It then remains more or less constant until digitalis is stopped. Nausea next develops and may appear in recurring "waves." The significance of nausea as an early indication of digitalis toxicity should not be discounted. Salivation often accompanies the nausea and at times, as Withering noted, it may be copious. Vomiting then occurs but at times it may develop without preliminary anorexia or nausea. This is especially likely to happen if large doses are given rapidly. The episodes of nausea and vomiting may start and stop abruptly, only to recur with greater severity. Nausea and vomiting may be transitory or entirely absent in some patients, and one should not rely on these signs alone to ascertain whether or not overdigitalization has occurred. The fact that the same digestive derangements are noted in patients with heart failure is, of course, no deterrent to the use of digitalis. Parallel with the restoration of compensation comes relief from the anorexia, nausea and vomiting due to heart failure.

Diarrhea may also be noted and rarely it may be the only gastro-intestinal manifestation of digitalis overdosage. The mechanism of the diarrhea is unknown but it may well be the same as that for vomiting. *Abdominal discomfort or pain* often accompanies the gastro-intestinal symptoms. The total dose of digitalis which must be given before nausea and vomiting appear varies greatly (1.25 to 8.5 grams of the powdered leaf) but in general is no different in normal patients than in those with heart failure. Once the drug is stopped, gastro-intestinal symptoms disappear in a few days. In a few patients with severe heart failure, optimal therapeutic effects of digitalis may not be obtainable unless amounts of the drug are given which for a time produce episodes of nausea and vomiting or other evidence of toxic action.

The *mechanism* of the nausea and vomiting caused by cardiac glycosides has been the subject of considerable investigation. In former years it was believed that gastric irritation from the crude drugs caused the symptoms, and this notion is still exploited by some firms who claim that their preparations are "non-emetic." It is clear, however, that vomiting occurs only late in the course of digitalization and can be produced both clinically and experimentally in animals by the parenteral administration of digitalis. Likewise it is demonstrable that vomiting movements result even though the entire gastro-intestinal tract has been removed. These observations definitely eliminate local irritation as a factor and place the mechanism somewhere in the nervous system, probably in the medullary emetic center. Hatcher and Weiss (1922) showed that digitalis does not act directly on the medulla to cause emesis, and that by sectioning the cardiac nerves in the cat vomiting can be abolished. They concluded that the drug excites the central vomiting mechanism only through afferent stimuli arising from the overdigitalized heart. These stimuli are carried mainly by way of the sympathetic afferent fibers but also to a certain degree by the vagi. Although this explanation has been challenged, the bulk of clinical and experimental evidence points to the fact that the *vomiting is reflex in origin* and arises neither from irritation of the alimentary tract nor from direct stimulation of the medulla. The exact site of origin of the afferent stimuli in man may require further elucidation. That the heart is the source has been seriously challenged by the experiments of Dresbach (1939).

Cardiac Effects. The alterations in cardiac rate and rhythm occurring in digitalis poisoning may simulate almost every known type of arrhythmia seen clinically. Before deciding whether digitalis or an exacerbation of the patient's disease is the cause, one must marshal all the available evidence concerning the nature of the heart disease, the cardiac status before the drug was given, the doses used and the response manifested during the period of digitalization. When sufficient information is not obtainable, the electrocardiogram may at times be helpful. In particular, the P-R interval and the character of the T waves may assist in deciding whether digitalis is responsible.

Extrasystoles. Probably the most frequent cardiac effect of digitalis overdosage is the occurrence of extrasystoles. These originate most commonly in the ventricle but can arise from the auricle. The cause of the ectopic beats is the increased irritability of the myocardium produced by excessive amounts of digitalis. If the extrasystoles are frequent, the ventricular rate increases and overshadows a primary slowing due to a toxic depressant action of the glycoside on the rate of impulse discharge by the S-A node. If the extrasystole recurs after each regular systole, digitalis "coupling" is present (pulsus bigeminus) (Figure 52). This is particularly likely to occur in patients with auricular fibrillation and fortunately permits the recognition of overdigitalization, because ventricular ectopic beats may sometimes be difficult to detect in this arrhythmia.

The occurrence of ectopic beats does not in itself always signify that digitalis dosage must be curtailed. In some patients relatively small doses may cause this sign to appear. The existence of extrasystoles before digitalis is given does not contraindicate the drug, which indeed may decrease the number of the abnormal beats.

Cardiac rate. Although the ventricular rate may be increased by digitalis if numerous extrasystoles appear, it may also be slowed either through a direct

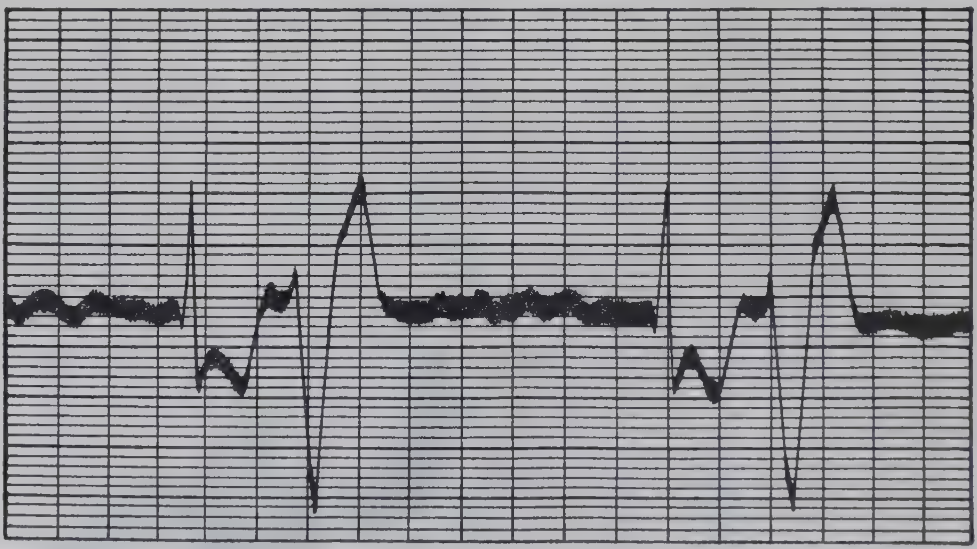


FIGURE 52. *Advanced digitalis intoxication.*

Male, aged 75, arteriosclerotic heart disease and auricular fibrillation. ECG: Lead 2. Note the marked depression of the RS-T segment in the "normal complexes" (the first and third), and the ectopic ventricular beat which follows each of these complexes. This is an example of "digitalis coupling." (Courtesy of Dr. A. J. Geiger, Yale University School of Medicine.)

action on the S-A pacemaker or on the A-V conduction system. Slowing due to a direct action of digitalis on the pacemaker requires very large amounts of the drug. Ventricular escape and rarely auricular standstill may result. Toxic amounts of digitalis may cause sufficient prolongation of A-V conduction to produce dropped beats and at times complete auriculoventricular dissociation (Figure 53). Lesser grades of depression of conduction do not result in cardiac slowing but higher grades occur with excessive doses of digitalis and often indicate previous disease of the conduction system. Partial or complete A-V block must always be viewed as evidence of the toxic action of digitalis. The usually accepted rule is to stop digitalis if the ventricular rate falls to 60 beats per minute or below. *It must be remembered, however, that the heart rate may not be slowed at all by digitalis and that an increase in rate may be the first evidence of digitalis poisoning.*

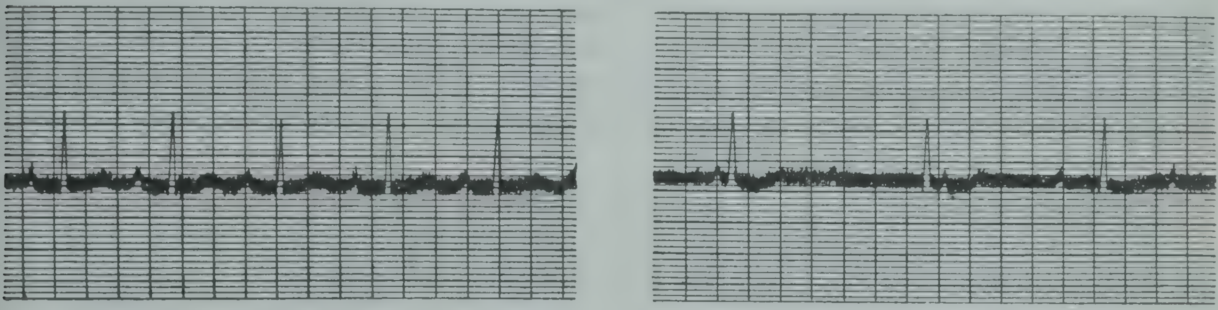


Figure 53. *Effect of digitalis on the conduction system.*

Female, aged 60, arteriosclerotic heart disease. ECG: Lead 1. *Left:* Before digitalis, incomplete A-V block; P-R interval, 0.24 second. *Right:* Same lead, after 2.0 grams digitalis in 18 days. Complete A-V block with dissociation of auricular and ventricular activity, presumably due to digitalis intoxication. Note that the previously upright T-wave has been replaced by a very shallow negative dip of the RS-T segment, also probably as an effect of digitalis. (Courtesy of Dr. A. J. Geiger, Yale University School of Medicine.)

Arrhythmias Due to Digitalis. Sinus arrhythmia occurs as an early and minor toxic effect of digitalis. It is noted especially in the young and can be abolished by atropine, signifying that vagal stimulation is probably the basis. *Paroxysmal tachycardias* from digitalis may arise either from the ventricle or auricle and call for discontinuance of the drug. *Auricular tachycardia* usually arises from an ectopic focus in the auricular muscle rather than from the S-A node. *Ventricular tachycardia* from digitalis is always serious and calls for immediate cessation of the drug because ventricular fibrillation may ensue. A particularly ominous type of ventricular tachycardia which is thought to signal the approach of fatal fibrillation of the ventricles is characterized by alternation in the direction of the Q-R-S complexes in the electrocardiogram (Marvin, 1928). Though this usually occurs in badly injured hearts, it is apparently specifically produced by digitalis (Figure 54).

Auricular fibrillation can be caused by large doses of digitalis (Tung, 1936). This result is sometimes sought in the therapy of auricular flutter. The occurrence of this arrhythmia usually but not always calls for temporary cessation of digitalis. That digitalis overdosage can cause fibrillation of the auricles is not a deterrent to the use of the drug in this disorder. *Ventricular fibrillation* is undoubtedly the commonest cause of death from digitalis poisoning. It is preceded by ventricular extrasystoles. Sudden death in patients receiving large amounts of the drug may well be due to this arrhythmia. It is particularly likely to occur from the injudicious use of large intravenous doses of the cardiac glycosides.

Other arrhythmias seen after digitalis include *pulsus alternans, heart block* and *auricular standstill.* The two last named have been mentioned.

Cerebral Effects of Digitalis. Headache, fatigue, malaise and *drowiness* are quite common symptoms of digitalis overdosage and occur early. *Mental symptoms* include disorientation, confusion, aphasia, and even delirium and hallucinations. *Convulsions* have been known to occur. Such effects are particularly likely to develop in elderly arteriosclerotic patients and the exact rôle played by digitalis is uncertain. Fishberg (1938) states that in his experience complicating factors of dehydration, fluid and salt restriction, vomiting, or diuresis from salyrgan have been present and that improvement occurred when ample fluids were given and the mercury and digitalis stopped. Also, digitalis has been demonstrated in edema fluid and it has been suggested that the toxic effects of the drug may suddenly appear when this fluid is mobilized in diuresis (Schnitker and Levine, 1937).

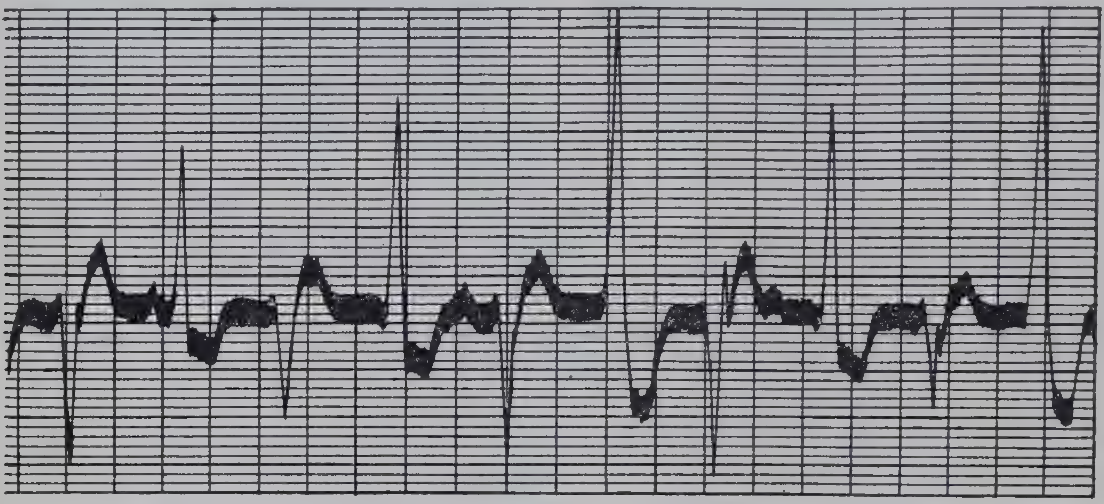


FIGURE 54. *Advanced digitalis intoxication.*

Male, aged 59, rheumatic heart disease with mitral and aortic stenosis and advanced congestive failure. Patient received 1.8 grams of digitalis in 24 hours. ECG: Lead 3, paroxysmal ventricular tachycardia with regular alternation in the direction of the ventricular complexes. Auricular rate, 94 per minute; ventricular rate, 138. Note especially the differences in size and shape of the ventricular complexes. Paroxysms of tachycardia like the one shown here recurred many times during the next four days and lasted from several minutes to several hours. The patient died four days after the tracing was taken. This type of arrhythmia is unusual and particularly ominous. Apparently it is seen only after excessive doses of digitalis. Marvin believes that the arrhythmia may represent ectopic beats arising alternately from the right and left ventricles. (After Marvin, 1928. Courtesy of the *American Heart Journal.*)

Vision. Vision is often blurred. White borders or halos may appear on dark objects ("white vision"). Color vision may be disturbed and objects appear yellow and green, or less frequently blue and red. Transitory amblyopia, diplopia and scotomata may also ensue. An explanation for these effects is not available.

Eosinophilia and Skin Rashes. These rare reactions to digitalis may be accompanied by refractoriness to the cardiac effects of the drug. The skin lesions may be urticarial or scarlatiniform in character. The increase in the number of eosinophils may be quite pronounced. Atropine has been known to lower the level of eosinophils and pilocarpine to elevate it (Romano and Geiger, 1936).

Bio-assay of Digitalis Preparations. Because the crude powdered leaf of digitalis varies in potency, physiological standardization of digitalis preparations is necessary. No acceptable chemical method of assay is yet available. Standardization is performed in several different ways.

The *official method* is that of the U.S.P. XI (1936) which requires that the digitalis be assayed on *frogs* and that the reference material used be a *Standard Reference Digitalis,* the strength of which, in relation to the *International Standard Digitalis Powder,* is known. This technic involves the injection of a suitably prepared tincture of the reference digitalis under standard conditions into the ventral lymph sac of frogs and the end-point is the systolic arrest of the ventricle in one hour. One *U.S.P. Digitalis Unit* or *International Digitalis Unit* is the equivalent of 0.1 gram of the International Standard Digitalis Powder. The B.P. also employs the International Digitalis Unit as its standard. Many objections have been raised to the U.S.P. frog method, among them being that a toxic action is measured and that the amphibian heart is far removed from the mammalian heart.

Other assays, not official in the U.S.P., have been devised and one commonly employed is the *cat method* of Hatcher and Brody. This involves the intravenous injection of the drug and the end-point is the death of the animal in one and one-half hours. The authors of the method discovered that the minimal lethal dose of ouabain for cats is almost uniformly 0.1 mgm per kg and that better results are forthcoming if ouabain is also injected. After a given amount of the unknown digitalis preparation has been administered, ouabain is given slowly until death occurs. The difference between the theoretical lethal dose of ouabain and the actual amount of ouabain used represents the part contributed by digitalis, the potency of which is then known in terms of ouabain. By this method, one *cat unit* represents the potency of an amount of digitalis which is lethal to one kg of cat.

Still other technics of bio-assay are used. Some are variants of the frog and cat methods described, and the units consequently vary with the particular modification employed. One of the better known modifications of the Hatcher and Brody cat method of assay is that of Magnus and Van Wyngaarden. This technic employs artificial respiration which permits the cat to tolerate a much larger dose of digitalis. The cat unit (Magnus) obtained by this assay thus represents a larger amount of drug than does the Hatcher-Brody cat unit. Other technics employ various species of animals. The *lethal dose assay in guinea pigs* and the *pigeon emesis method* are two which have received particular attention.

Unitage. It is important for the clinician to appreciate the change in digitalis unitage (and hence dosage) brought about through the adoption by the U.S.P. XI of the International Digitalis Powder as the standard of potency. This occurred as a result of a desire to conform to international standards of drug potencies as urged by the League of Nations Health Committee. The International Digitalis Powder proved stronger than the U.S.P. X digitalis which was official between 1926 and 1936. As a result, *U.S.P. XI digitalis is from 25 to 30 per cent stronger than the U.S.P. X digitalis and the dose must therefore be reduced proportionately, that is, by about 20 per cent* (Edmunds, 1939).

Digitalis dosages referred to in the clinical literature between 1926 and 1938 are largely based on U.S.P. X digitalis. Now that the U.S.P. XI digitalis is available on the market, it is essential to appreciate that the doses formerly prescribed (U.S.P. X) are too large by about one-fifth and that overdosage and digitalis intoxication may result unless confusion is avoided. Reports of overdigitalization have already appeared due to this error. The difficulty lies in the fact that a considerable amount of U.S.P. X digitalis is still being marketed. It is incumbent upon the physician to know the potency of the digitalis which he is employing and the method by which it was standardized, and a patient whose optimal maintenance dose is well regulated on one product cannot be shifted indiscriminately to another preparation of different potency. If the cat unit is preferred to the U.S.P. digitalis unit, one must know the potency of the particular cat unit which is used.

An important point to bear in mind is that bio-assay is subject to considerable variation and that two methods of digitalis assay may give discordant results when compared with each other. For this reason, the Council on Pharmacy and Chemistry does not require pharmaceutical firms to assay their digitalis preparations by two different methods, and the N.N.R. includes drugs assayed by any single method acceptable to the Council. The physician may therefore expect to find some variation in potency between different commercial products, and he would do well to restrict his choice to a single preparation or a few satisfactory preparations, with which he has become familiar, rather than to use without discrimination a large number of digitalis preparations and purified principles which are available. *In the last analysis, clinical assay of any particular product must be done on the patient.* Individuals vary so greatly in their response to and requirement of digitalis that one must look to the patient in order to determine the dose of digitalis.

The term "cat unit" is becoming more and more ambiguous and confusing, and it would probably be best if digitalis potencies were always expressed in terms of official U.S.P. units. However, inasmuch as many firms assay and market digitalis products in terms of "cat units," many physicians have become accustomed to think in terms of these units when prescribing for patients. The "cat unit" derived by the original Hatcher-Brody assay fortuitously represented almost the exact amount of digitalis in 0.1 gram (powder) or 1.0 cc (tincture) of U.S.P. X digitalis. This fact allowed physicians a ready interconversion between "cat units" and 0.1 gram or 1.0 cc doses of U.S.P. X digitalis. For example, when it was finally established by the Council in 1924 that 1.5 grams (15 cc) of digitalis were essential for initial digitalization in the average patient, this same dose was referred to as 15 "cat units." Similarly, the average maintenance dose of digitalis of 0.1 gram (1.0 cc) once or twice daily was translated into one or two "cat units" daily. Due to the many variations of the original Hatcher-Brody method, however, and the resulting multiplicity of "cat units," one cannot assume that an amount of digitalis representing the "cat unit" of one drug distributor is exactly the same as that of another, unless identical methods of assay are known to be employed. The interconversion between "cat units" and U.S.P. digitalis units has become more difficult due to the increased potency of U.S.P. XI digitalis as compared with the U.S.P. X. Indeed, such interconversion serves no useful purpose. The original Hatcher-Brody cat unit has not changed because the sensitivity of cat hearts to the glycoside has not changed but the amount of digitalis powder which it represents depends upon whether it is being measured in terms of U.S.P. X or U.S.P. XI digitalis.

Preparations Available for Clinical Use. Many digitalis and digitalis-like drugs are available to the physician. It may be said at the outset that the safest method of administering digitalis is to use a well-standardized tincture or powdered leaf. Withering, after exhaustive trials of various foxglove preparations, finally decided on the powdered leaf. All digitalis-like drugs manifest the same type of cardiac activity and it has not been conclusively demonstrated that the various digitalis substitutes or fractions have any clinical advantage over the galenical preparations. Another important point is that of cost, because digitalis medication must often be continued for years and the purified proprietary products are quite expensive. Preference should be given to the official U.S.P. and B.P. preparations of digitalis. Galenical preparations act quickly and effectively, are readily available and relatively inexpensive. They can be prescribed as the official tincture or powdered leaf.

Powdered Digitalis, U.S.P., B.P. The source, composition, assay and unitage of powdered digitalis leaf have been described. When "digitalis" is prescribed without further designation, the official powdered leaf is dispensed by the pharmacist. The powder can be administered in pill, tablet, capsule or suppository form.

Tincture of Digitalis, U.S.P., B.P. This is the only acceptable liquid preparation of digitalis. One cc of the tincture is equal in potency to 0.1 gram of powdered digitalis (one U.S.P., B.P. or International Digitalis Unit). The *Infusion of Digitalis* (N.F.) is an unstable aqueous preparation which should not be employed.

Strophanthus, N.F., B.P. The source and composition of strophanthus have been described. It has no advantage over digitalis and is seldom used. The intestinal absorption of powdered strophanthus and the *Tincture of Strophanthus* (N.F., B.P.) is unpredictable, and diarrhea is frequently noted after their ingestion. Galenical preparations of strophanthus have no place in modern therapy.

Squill, U.S.P., B.P. The use of squill or any of its official galenical preparations, such as *Syrup of Squill, Tincture of Squill* or *Fluidextract of Squill,* is obsolete. The source and composition of squill have been discussed.

In addition to the galenical preparations listed, purified glycosidal fractions of digitalis, strophanthus and squill are also available. Many of these are water-soluble and are advantageous when parenteral therapy is necessary. The official and more important of the N.N.R. purified fractions are as follows:

Strophanthin, U.S.P., B.P. (K-Strophanthin). This represents a mixture of glycosides obtained from *Strophanthus kombé* (Table 29). It consists of a white or yellowish powder which is soluble in water. Strophanthin is marketed in hypodermic tablets containing 0.3 or 0.6 mgm each. The drug is assayed in a manner identical with that for digitalis except that ouabain is employed as the reference material. Strophanthin is adjusted to have from 40 to 60 per cent of the potency of an equal weight of ouabain.

Ouabain, N.N.R. (Crystallized strophanthin, g-strophanthin). Ouabain is a crystalline glycoside obtained from *Strophanthus gratus.* Its chemistry has been described (Table 29). Ouabain is a reference standard in the U.S.P. and B.P., but is not in itself official. It is so slowly and irregularly absorbed from the intestinal tract that its oral use is unsafe. It is of value for parenteral administration, however, and being water-soluble it is marketed in sterile buffered solution in ampules containing 0.25 or 0.5 mgm per cc.

Digitoxin, N.N.R. Digitoxin is a purified glycoside obtained from *Digitalis purpurea* and is the chief active ingredient of digitalis, Its chemistry has been described (Table 29). Digitoxin is a colorless crystalline material, slightly soluble in water, and is marketed in tablet form for oral use and as a powder for rectal administration.

Scillaren-B, N.N.R. This preparation contains the amorphous component of the mixture of glycosides occurring in squill (Table 29). It is a water-soluble powder marketed for parenteral administration in sterile solution in ampules containing 0.5 mgm per cc. *Scillaren,* N.N.R., is essentially a mixture of scillaren-A and scillaren-B, and is marketed for oral administration in tablets (0.8 mgm) and solution (0.8 mgm per cc). *Urginin,* N.N.R., likewise is a preparation of squill glycosides for oral use and is marketed in tablets (0.5 mgm) and solution (1.0 mgm per cc).

Other N.N.R. purified proprietary preparations of digitalis leaf include *Digalen* (tablets and solution for oral use, and ampules for injection); *Digifoline* (tablets and solution for oral use, ampules for injection); *Digitalin* (French and German varieties; glycosidal mixtures not to be confused with the pure glycoside of the same name); *Gitalin* (said to be the purified glycoside of the same name; tablets for oral use). The descriptions of these appear in N.N.R.

The burden of proof that any of the digitalis substitutes or purified fractions is more valuable than the tincture or powdered leaf of digitalis lies squarely on the manufacturer making such a claim. Clinical evidence is against such contention. Furthermore it is misleading to insist that some of these drugs are less toxic or less emetic than others. The toxic actions of the cardiac glycosides are merely extensions of their therapeutic effects. The potency or toxicity depends not on the degree of purification but on the amount of drug given to the patient.

Stability of Digitalis Preparations. Powdered digitalis obtained from adequately dried leaves will keep for many years (16 in some cases) without significant loss of potency. The official tincture of digitalis, although not as stable as the powdered leaf, is still useful several years after preparation. When marketed in soft glass ampules, aqueous solutions of glycosides, such as ouabain or strophanthin and injectable digitalis fractions, eventually undergo deterioration from the alkalinity of the container. Hard glass or phosphate buffered solutions are therefore desirable. The powdered leaf, it appears, is superior in stability to any liquid preparation of digitalis (Haag, 1938).

Absorption, Fate and Excretion of Digitalis. *Absorption.* Digitalis given orally is adequately absorbed from the intestinal tract. The stomach does not participate in this absorption and the effect of the gastric juice on the drug is negligible. Local irritation is avoided by taking the drug with meals. Digitalis is well absorbed under nearly all circumstances, including chronic passive congestion of the enteric mucosa due to heart failure. Strophanthus and squill, on the contrary, are so irregularly absorbed that their oral use is dangerous and obsolete.

A single dose of digitalis is usually entirely absorbed within two hours and exerts its full action on the heart within six hours. This fact determines the interval between doses when the patient is being digitalized by the rapid method. Electrocardiographic evidence of initial myocardial action is detectable within two hours after a large oral dose of digitalis. That orally administered digitalis may not be completely absorbed, however, is suggested by the fact that smaller intravenous than oral doses are needed to produce comparable effects on the heart. When the glycosides are given by *vein,* initial cardiac action is noted within five to 15 minutes.

When given *subcutaneously* or *intramuscularly,* even purified digitalis preparations cause considerable pain and local reaction. Sterile abscesses may result and absorption is uncertain. Digitalis is readily absorbed from the lower part of the large bowel and *rectal instillation* therefore offers a valid means of administration if the drug cannot be taken orally.

Fate. The fate of digitalis in the body is unknown. The extracardial tissues, especially the liver and skeletal muscles, take up over 90 per cent of the drug mainly because of their bulk. Gram for gram, the heart muscle is thought to absorb more of the glycoside than any other organ of the body. Hatcher and Eggleston, (1919), however, were unable to demonstrate a selective storage of ouabain in any particular organ or tissue and are inclined to believe that a fairly uniform distribution of the glycoside occurs in the body.

Excretion. Digitalis is eliminated slowly from the body. With repeated doses, therefore, cumulative effects occur and eventually result in digitalis poisoning. After cessation of the drug, the cardiac actions persist for several days to three weeks or more. It is thus essential to know whether, when and how much digitalis has previously been given to a patient before administering additional drug. Strophanthin, in contrast to digitalis, is eliminated more rapidly so that the effects of a single full dose are dissipated in two to five days. It appears probable that thevetin is one of the most rapidly eliminated of the cardiac glycosides. The exact rate of excretion of digitalis is discussed later in connection with the maintenance dose.

The relative importance of destruction of cardiac glycosides in the body as compared with their excretion is unknown. Some of the drug is excreted unchanged in the bile and the urine but this represents only a small fraction of the total amount given.

Routes of Administration. *Oral.* The oral route of administration is used whenever possible. It is the least expensive and the safest, and absorption is sufficiently rapid so that early beneficial cardiac effects can be anticipated within two to six hours after large doses. Digitalis is usually given at meal time either as the tincture or as the powdered leaf in pill, tablet or capsule form.

Parenteral. The hypodermic injection of digitalis preparations is not advised due to the pain, local reactions and poor absorption characterizing this route of administration. When parenteral digitalis is necessary, the intravenous route is selected. This is only warranted when minutes rather than hours may spell the difference between life and death. Patients requiring intravenous digitalis are therefore moribund, and emergency measures such as venesection have failed to establish improvement. The preparations used are the strophanthin glycosides or the water-soluble, purified digitalis fractions. It is preferable to dilute the drug in isotonic sodium chloride solution and the injection is made *very slowly.* The dose must be carefully calculated and the facts concerning previous digitalis medication must be known. The intravenous route is by far the most dangerous and acute fatality may result from its use. Furthermore, the administration of parenteral preparations does not have the background of the large amount of clinical experience which has accumulated for the oral route of digitalis medication.

Rectal. If digitalis cannot be given orally, rectal administration is a satisfactory substitute. This may be needed especially if the patient is vomiting. A cleansing enema is given and the digitalis is then delivered through a small rectal tube. The preparations used rectally are the tincture of digitalis, diluted 1:7 so that the alcohol will not be irritating, or one of the Council-accepted water-soluble digitalis preparations (parenteral). Suppositories of powdered digitalis may also be employed. The doses, intervals between doses, and the time necessary for obtaining cardiac effects are the same for rectal as for oral digitalis medication.

Dosage: For Initial Digitalization. Digitalis dosage includes two problems, the amount needed to obtain therapeutic effects in a patient not previously receiving the drug (initial digitalization) and the amount needed to maintain these effects (maintenance dosage). Withering wrote, "I give to adults, from one to three grains of this powder twice a day. . . . About thirty grains of the powder . . . may generally be taken before the nausea commences." It is clear that the father of digitalis therapy understood that early toxic effects occurred when two grams (30 grains) of the powdered digitalis leaf were taken in the course of a few days.

In 1915, Eggleston radically changed the prevailing concepts of digitalis therapy by demonstrating that cardiac effects of the drug could be obtained within a few hours if large oral doses were used. Up to that time it was considered that several days were necessary before digitalization could be accomplished. Eggleston showed that full therapeutic or minor toxic effects appeared when about 15 (original Hatcher-Brody) cat units (15 cc of the U.S.P. X tincture; 1.5 grams of the U.S.P. X leaf) were given per 100 pounds of body weight. For the average 150 pound individual this dose would be approximately 20 cat units (20 cc tincture; 2.0 grams of the leaf). This could be given in divided doses over a period of one or two days dependent on the urgency of the case. It soon became apparent, however, that this dose level was somewhat high and represented an average that was not to be exceeded, rather than an optimal amount. Furthermore, body weight offered many obstacles to the calculation of dose by formula. Weighing the patient in the home is often impossible and it is not always easy to determine the edema-free weight.

A few years later, therefore, the report of the Council (1924; prepared by Robinson, White, Eggleston and Hatcher) established the following oral dose of digitalis which is the accepted practice today: "The total average dose of fairly active standardized digitalis by mouth for inducing full therapeutic effects within thirty-six to forty-eight hours in an adult who has not received digitalis within ten days is about 1.5 grams (=1.2 grams U.S.P. XI) * of the leaf or 15 cc (=12 cc U.S.P. XI) * of the tincture. The total dose may be divided into several equal parts given every four or six hours, or one-half or one-third of the total calculated dose may be given at once, and the remainder in two portions after intervals of four to six hours." It will be noted that no mention is made of body weight and that the rapidity of administration depends upon the patient's condition. If severe decompensation is present and digitalis has not been taken for the previous two weeks, one-third of the total dose (0.4 gram of the powdered leaf, U.S.P. XI; 0.5 gram, U.S.P. X) may be given immediately and repeated at six and again at 12 hours. The dose is then dropped to 0.08 to 0.16 gram, U.S.P. XI (0.1 to 0.2 gram, U.S.P. X) two or three times daily until optimal benefit is obtained and the maintenance dose can be adjusted. If one still feels that body weight is important and that a heavy patient requires more than the 1.2 grams of U.S.P. XI digitalis (1.5 gram, U.S.P. X), suggested above for initial digitalization, the dose level of 0.08 gram of powdered leaf, U.S.P. XI (0.1 gram, U.S.P. X), for each 10 pounds of body weight can be used.

If the physician is uncertain of the amount of digitalis taken by the patient within the previous week or two, the large doses outlined cannot safely be given. It is then best to administer 0.16 gram of the U.S.P. XI leaf (0.2 gram, U.S.P. X), three or four times daily and observe the patient closely for signs of intoxication before each subsequent dose is given. An interval of six to eight hours usually allows sufficient time for a single dose to take effect.

Intravenous Dosage. In the rare instances in which beneficial results must be obtained in minutes rather than in a few hours, intravenous medication may be given. In patients who have not received digitalis for two weeks, 0.25 to 0.5 milligram of *ouabain* or *strophanthin* may be injected. Rarely need this dose be repeated and it is best to complete the digitalization by giving 0.24 gram of the leaf, U.S.P. XI (0.3 gram U.S.P. X), orally every six hours until full benefit is secured. An alternate procedure is to continue with intravenous doses of 0.1 mgm of ouabain or strophanthin every half-hour until a total of 1.0 mgm of the glycoside has been injected. Oral or rectal medication, however, should be instituted as soon as possible. Cardiac glycosides must not be given intravenously to patients in whom a careful study of the heart has not been possible or who have been receiving digitalis within the previous 10 days.

Doses for Children. It is usually stated that children require more digitalis per pound than do adults, and that from 50 to 100 per cent more drug than calculated on the basis of body weight must be given to obtain results. As has been emphasized by Luten (1936), however, such estimates arise from the fact that heart failure in children is often an expression of active rheumatic carditis in which digitalis even in large doses may produce little benefit. Furthermore,

* Authors' insertion.

Luten points out that these large doses are often productive of toxic symptoms. It therefore appears that the type of heart disease rather than the age of the patient modifies the dose of digitalis required and that age itself is of secondary importance. Eggleston's studies also failed to reveal age as a significant factor in digitalis dosage, nor was sex found to be an important consideration.

Dosage: For Maintenance. Most patients receiving digitalis continue to require the drug for the remainder of their lives. It is therefore necessary to give digitalis daily in order to maintain the beneficial effects realized by the original digitalization. This requires that a sufficient amount be given to replace that which is destroyed or eliminated by the body.

Various attempts have been made to calculate this maintenance amount in order to arrive at an acceptable average daily dose of digitalis. Pardee (1919) gave digitalis to patients until emesis occurred, then stopped the drug for a few days and finally gave enough again to cause vomiting. The difference between these two amounts divided by the days during which no drug was administered gave a calculated average excretion rate of 1.2 cat units (approximately 1.2 cc or 0.12 grams, U.S.P. X) per day. Variations of from −55 per cent to +82 per cent, however, were noted. With a similar technic but employing electrocardiographic evidence of a definite level of digitalis action, Bromer and Blumgart (1929) arrived at an average daily excretion rate equal to a little over 1.5 cat units. From studies of this nature the statement has gained acceptance that the average adult excretes daily an amount of digitalis contained in 1.2 cc of tincture or 0.12 gram of powdered leaf, U.S.P. XI (1.5 cc or 0.15 gram, U.S.P. X), and that this amount therefore represents an average maintenance dose.

It was clearly established by the above investigations, however, that wide variations existed from patient to patient and that the maintenance dose bore no relation to body weight or to the type or severity of heart failure. Furthermore, subsequent studies showed the rate of excretion varied not only from person to person, but also in the same individual depending on the amount of drug in the body. The work of Gold and De Graff (1929, 1930) indicates clearly that the patient excretes not a fixed amount each day regardless of the dose given but rather a certain fraction of the amount present in the body. These investigators further pointed out that the rate of elimination tends to be a self-limiting process. If digitalis is started at a moderate dose level, the excretion rate is minimal at first and some of the drug accumulates in the body. As medication continues and more drug accumulates, the rate of elimination increases until equilibrium is reached, at which point excretion balances intake. Acceleration of excretion rate is definitely limited, however, and with excessive doses the drug accumulates in the body to the point where toxic symptoms occur.

That a fixed amount of digitalis is not excreted or destroyed daily but that increasing increments are eliminated as the drug accumulates in the body can readily be appreciated by consideration of the following example. Suppose that a patient who has not received digitalis previously is given 0.1 gram of the powdered leaf three times daily and full digitalization occurs on the fourth or fifth day. Suppose also that this patient is then found to require this same dose for maintenance therapy. It must be assumed that he is then excreting or destroying each day 0.3 gram of digitalis leaf, or intoxication would soon occur. If he eliminated daily this same fixed amount of drug during the initial few days of therapy, it obviously would not have been possible to digitalize the patient with the dose employed.

It is therefore impossible to employ any rule of thumb in reaching a daily maintenance dose of digitalis. The amount required varies with each case and depends upon the level of digitalis action desired. This level is usually that which allows *optimal digitalis effects.*

The Concept of Optimal Digitalis Effect and the Dose Necessary tc Maintain It. After the patient has been initially digitalized and optimal benefit obtained, the dose is adjusted to maintain this level of digitalis action. Most patients require about 0.8 cc of the tincture or 0.08 gram of the powdered leaf, U.S.P.XI (1.0 cc, 0.1 gram, U.S.P.X) once or twice daily. Others, however, may need as little as one-third or as much as four times this amount daily. It is important to understand that in most patients the optimal dose is definitely below that which will cause early toxic effects. It is therefore not necessary to increase the dose to the point of producing nausea and vomiting in order to find the optimal maintenance level.

In other words the ideal dose is not necessarily the largest dose tolerated. An amount is sought which will restore the highest degree of cardiac efficiency and relieve all symptoms and signs of heart failure. This dose is discoverable not by formula or in the electrocardiogram but in careful daily observation of the patient. It may be large or small and varies in the same patient according to changes in the condition of the myocardium. In some patients, especially those with severe heart failure, the optimal dose occasionally for a time may border on the toxic, and beneficial results will be obtainable only with amounts of digitalis which produce early symptoms of poisoning.

If the tincture is employed, calibrated medicine glasses or medicine droppers must be used to insure accurate dosage. The difference between minims and "drops" is particularly important in prescribing the small daily maintenance doses of tincture of digitalis. One can employ the isoalcoholic elixir to advantage by prescribing it as a vehicle for the tincture of digitalis so that a suitable dose of the latter is contained in each four or five cc of the mixture. A teaspoon or standardized vial known to hold this amount is then used by the patient and an exact dose of digitalis obtained in this manner (page 1321).

Therapeutic Indications for Digitalis

The Foxglove's leaves, with caution given,
Another proof of favouring Heav'n
Will happily display;
The rapid pulse it can abate;
The hectic flush can moderate
And, blest by Him whose will is fate,
May give a lengthen'd day.
William Withering.

Congestive Heart Failure. By far the most important use of digitalis is in congestive heart failure. The devious route by which this single clear-cut indication for the drug finally became definitely established has already been traced. Digitalis is useful regardless of whether the failure is predominantly of the left or right ventricle, or involves both sides of the heart. The type of rhythm exhibited by the decompensated heart neither indicates nor contraindicates the use of digitalis and the same statement holds true for valvular defects. Arrhythmias and valvular lesions may modify the response to, but they do not alter the indication for, digitalis if failure is present. In the last analysis, improvement of cardiac function by digitalis depends on the myocardial reserve. In badly damaged hearts, therefore, digitalization may not produce much benefit.

While it is true that the most dramatic responses are seen in patients with congestive heart failure and auricular fibrillation, excellent and equally significant results are obtained in cases of failure with normal rhythm and rate (Figure

50). Exertional and paroxysmal nocturnal dyspnea, cough, cyanosis, ascites, edema, and chronic passive congestion of the lungs and abdominal viscera are relieved. Diastolic size of the heart is decreased; venous pressure is lowered to normal; cardiac output, stroke volume and circulatory velocity are enhanced; and the diastolic rest period in each cardiac cycle is prolonged.

The rate of the ventricle may or may not be slowed. If tachycardia is present as a compensatory mechanism due to the failure, the rate of the heart slows as digitalis restores the functional efficiency of the ventricle toward normal. If auricular fibrillation is present, digitalis usually will slow a rapid ventricular rate only if the tachycardia is secondary to heart failure (Luten, 1936; Luten and Jeffreys, 1936).

The mechanism by which the direct myocardial action of digitalis brings about the restoration of cardiac compensation has been discussed. Once digitalis has returned the failing heart to a state of compensation, its continued use will do much to prevent the recurrence of heart failure.

Etiology of Heart Failure as a Modifying Influence on Digitalis Action. It is well known that the best results with digitalis are obtained when failure occurs in *hypertensive* or *arteriosclerotic* hearts. In decompensation due to *severe rheumatic myocarditis,* digitalis may give little or no relief. It has already been mentioned that digitalis may fail to restore compensation in children and this is due to the fact the rheumatic heart disease is prevalent in the young. Heart failure secondary to *cardiovascular syphilis* yields poorly to digitalis, especially if syphilitic aortitis is present. This is probably explained on the basis of the involvement of the coronary ostia by the syphilitic lesion. In other *infectious or toxic myocarditides,* such as diphtheritic heart disease, digitalis is not only ineffective but may actually be contraindicated. Heart failure occurring in *myxedema, hyperthyroidism,* and *thiamine deficiency* is not aided materially by digitalis.

In the so-called "heart failure" secondary to *shock,* and in *hypodiastolic failure* (Fishberg, 1938) due to cardiac compression from pericardial effusion or constricting adhesions, digitalis is of no value. The disturbance in function is not in the myocardium and the heart is involved only secondarily. In shock, digitalis may further decrease cardiac output and thus aggravate the syndrome. This also holds true for the type of *peripheral circulatory collapse* occurring in the course of acute infectious diseases.

Use of Digitalis to Prevent Heart Failure. Some authorities, notably Christian (1933), advocate digitalis as a prophylactic measure for patients in whom ultimate heart failure is a likely occurrence, especially elderly people with cardiac enlargement or hypertension. This promising field has been so little explored that sufficient clinical data are not yet available to decide on the value of digitalis as a preventive of heart failure. Also it should be remembered that the glycoside may decrease cardiac output in some patients with organic heart disease when heart failure is not present and this action may be detrimental to the patient (Stewart and associates, 1938). Many cases of auricular fibrillation with tachycardia, showing a minimal amount of failure and no discernible cause for the arrhythmia, are probably due to very early and occult decompensation of the ventricle. This etiology is particularly suggested if digitalis causes slowing of the heart rate. In such patients, the drug is undoubtedly valuable.

Auricular Fibrillation. This arrhythmia was at one time thought to be the main indication for the use of digitalis. It is now recognized, however, that the drug should be given only if heart failure is the cause of or accompanies the fibrillation. Cardiac failure and not the disorder of rhythm calls for digitalis. Indeed, if the disorder is due to toxic causes digitalis must be used with care, and even though decompensation is present the drug may fail to exhibit salutary effects. In some cases in which no cause can be found for the auricular fibrillation, digitalis may be used as a therapeutic test. If considerable slowing of ventricular rate occurs, occult failure as the basis of the arrhythmia is highly probable. Congestive cardiac failure is the most common cause of auricular fibrillation, however, and it is in such cases that digitalis is indicated and produces its most dramatic results.

The aim of digitalis therapy in auricular fibrillation with heart failure is to restore myocardial efficiency and an optimal ventricular rate, and to eliminate the pulse deficit (Figure 50). The mechanism of ventricular slowing by digitalis in this disorder has been fully discussed. If failure is not present, little effect on the ventricular rate will be noted, particularly in toxic cases where the drug may even be harmful. The decision to use the glycoside is therefore modified not only by the presence or absence of failure but also by the presence or absence of a toxic basis for the fibrillation. Digitalis is particularly needed in non-toxic cases with failure; it may be contraindicated especially in toxic cases without failure, as in thyrotoxicosis and diphtheritic heart disease.

The fibrillation of the auricle is not halted by digitalis. The auricular rate may increase or decrease but it is usually speeded both by the muscular and vagal effects of digitalis. Both digitalis and quinidine increase the refractory period of and slow the rate of conduction in auricular muscle but accomplish this by entirely different means. It may be asked legitimately, therefore, why digitalis does not stop auricular fibrillation. The answer must lie in the fact that the glycoside does not sufficiently lengthen the refractory period of auricular muscle to interrupt the circus movement. Such an action of digitalis can arise only from an increase in the force of auricular contraction. Digitalis may not be able to accomplish this in a dilated fibrillating auricle. Furthermore, larger doses increase muscular irritability and thus shorten the refractory phase. Likewise vagal stimulation caused by the drug also tends to shorten the refractory period. These combined effects fix and perpetuate, if not actually accelerate the rate of, the auricular fibrillation. Therefore the action of digitalis on the ventricle, not on the auricle, is sought in this disorder.

Auricular Flutter. Digitalis has the same indications and mechanism of action in auricular flutter as in auricular fibrillation, and the foregoing discussion of the latter arrhythmia applies here. The ventricular rate is slowed if failure is present, but in addition the action of digitalis on the conduction bundle comes into play as previously described.

It is sometimes possible to convert the flutter to fibrillation by large doses of digitalis. This is accomplished by combined muscular and vagal effects of the drug to shorten the refractory period of auricular muscle and therefore to increase the rate of circus movement. The large doses needed for this purpose usually result in toxic symptoms and cause a high grade of A-V block reaching 4:1 or higher. The ventricular rate may fall to 60 or below. As soon as the flutter has been converted to fibrillation, the digitalis is stopped whereupon normal sinus rhythm may be established. This is thought to be due to the fact that a recently produced fibrillation tends to stop when the exciting cause is removed. In this instance, the exciting cause is digitalis. In many cases, however, the fibrillation persists or reverts to flutter. In any event, the slower ventricular rate is beneficial. If auricular flutter or fibrillation persists, chronic medication with digitalis is adopted to maintain an optimally efficient ventricular rate.

Paroxysmal Tachycardia. Although digitalis can produce this disorder as a toxic effect and should be stopped when it occurs, nevertheless in certain cases of supraventricular (nodal or auricular) origin the drug may successfully terminate an attack. The tachycardia is first slowed and then aborted. Mecholyl and carotid sinus pressure, however, are to be tried first. If these fail, quinidine may be employed before digitalis is used. Digitalis should not be prescribed if tachycardia is of ventricular origin. The necessity for terminating an episode of tachycardia lies in the fact that, if prolonged, heart failure and death may occur.

Special Factors Modifying Digitalis Therapy

Coronary Thrombosis. Coronary occlusion in itself is not an indication for digitalis. Digitalis is contraindicated during the first few days following an acute coronary thrombosis. The clinical picture is usually one of shock rather than congestive heart failure, and digitalis, by further decreasing cardiac output, may make the patient worse. Again, the injured myocardium is quite irritable as evidenced by the occurrence of ectopic beats and abnormal rhythms. Under these circumstances digitalis may further increase the irritability of the myocardium and there is danger of precipitating ventricular tachycardia or fibrillation. It is also believed that the strong ventricular systoles promoted by the drug may strain the infarcted and friable myocardium undesirably, or tend to dislodge mural thrombi and thus cause embolism of pulmonary or systemic vessels. Digitalis is therefore not recommended unless progressive congestive failure ensues.

The dosage of digitalis in patients with acute coronary thrombosis must be carefully regulated, and rapid digitalization is usually unwise. There is some experimental evidence indicating an increased sensitivity of the injured myocardium to digitalis (Travell, Gold and Modell, 1938), and the drug should be given only in moderate amounts in order to meet this decreased tolerance. A reduction in dosage of at least 25 per cent should be observed until the patient's response is learned.

Angina Pectoris. Both experimental and clinical data apparently show that digitalis does not decrease coronary blood flow when given to man in therapeutic amounts. Indeed, in patients with heart failure, the restoration of efficient heart action may improve coronary circulation. Digitalis is not indicated in angina pectoris without heart failure. If failure is present, the coexistence of angina pectoris does not contraindicate digitalis. Cases have been reported in which digitalis was thought to have increased the frequency of attacks of pain. The explanation for this may be that cardiac output is probably decreased by the drug when failure is absent. It is also possible that digitalis, by restoring cardiac compensation in patients with angina pectoris and heart failure, allows a sufficient increase in physical activity to precipitate anginal attacks. It is well known, for example, that attacks of anginal pain are likely to disappear when congestive failure ensues, probably as the result of the restricted activity which decompensation imposes. The thorough studies of Gold and coworkers (1938) already referred to, however, do not allow the dogmatic conclusion that the drug directly influences either the incidence or severity of anginal attacks.

Pneumonia. There is no justification for the routine use of digitalis in pneumonia. The rapid heart rate, cyanosis, dyspnea, and other cardiovascular symptoms, as a rule, are not the result of cardiac decompensation. The heart is affected by the general toxemia and, unless there is failure, digitalis may do harm. The evidence strongly indicates that when digitalis is used routinely in patients with pneumonia, the mortality rate is definitely increased, and this fact applies as well to cases complicated with auricular fibrillation (Wyckoff and collaborators, 1930). Unless the incontrovertible indication exists for its employment, namely, congestive cardiac failure, digitalis should be withheld in pneumonia.

Thyrotoxicosis. The existence of hyperthyroidism in itself is not an indication for digitalis therapy. Tachycardia due to hyperthyroidism either with or without auricular fibrillation does not yield to digitalis therapy because it results from the action of the thyroid hormone on the heart and is not secondary to myocardial insufficiency (Figure 47). If heart failure is present, the drug is given just as if there were no thyrotoxicosis. The former practice of routinely digitalizing thyrotoxic patients before operation is losing favor. Rest in bed and medication with iodides and sedatives prior to thyroid resection usually have the desired salutary effect on the tachycardia. If auricular fibrillation occurs and persists despite surgical relief of hyperthyroidism, quinidine may be indicated.

Diphtheria. The heart injured by diphtheria toxin is more susceptible to digitalis and may be further harmed by the glycoside. If congestive failure is present in diphtheritic hearts, digitalis must be used with caution and in smaller dosage than usual. The drug in no way protects the heart against diphtheria toxin, is not indicated unless decompensation occurs, and offers little therapeutic promise.

Arrhythmias. There is no particular rhythm of the heart which indicates or contraindicates the use of digitalis. If heart failure is present, digitalis should be prescribed regardless of cardiac rhythm. The use of digitalis in the presence of paroxysmal tachycardia and fibrillation or flutter of the auricles has been discussed. In the presence of *partial heart block,* the drug may cause complete heart block but may be used if decompensation exists. Indeed, Blumgart and Altschule (1939), in a study of 19 patients with preexisting heart block, showed that digitalis can be given safely and optimal benefit obtained with doses which do not increase the grade of block. In *complete heart block* (auriculoventricular dissociation), digitalis may be employed safely and is indicated provided failure has occurred. The dosage used is often somewhat lower than that employed when block is not present. The idiopathic ventricular rate is usually not accelerated unless toxic amounts are given.

Valve Defects. There is no specific valve defect which indicates or contraindicates the use of digitalis. The status of the myocardium and not the valve lesion determines whether the drug is to be prescribed. The prejudice against using digitalis in aortic insufficiency had no basis in fact.

It is true that poorer results are obtained in heart failure associated with aortic lesions than with mitral lesions. Yet this may be explainable in part by the fact that many cases of mitral disease are rheumatic in origin and have auricular fibrillation accompanied by failure. These patients respond well to digitalis. On the other hand, a number of the cases of aortic insufficiency are due to syphilis and respond poorly to digitalis. The relative refractoriness of syphilitic hearts to digitalis has been mentioned.

Other Drugs. *Calcium.* Cases of sudden death have been reported from the intravenous injection of calcium salts in digitalized patients. Although the full significance of these reports or of the experimental work on the possible synergistic action of the two drugs cannot be stated, it appears safest for the present to use calcium by the intravenous route very cautiously if at all in patients receiving digitalis. If the cation is needed by vein, it should be injected very slowly. Several studies, however, seem to indicate that the effects of calcium and digitalis are neither potentiative nor even completely additive (Smith, Winkler and Hoff, 1939). The actions of calcium on the heart are presented elsewhere.

Ephedrine. There is some evidence that ephedrine and digitalis given together may prove more toxic than when the same dose of either is used singly. Until more information is available on this point, it seems wise to proceed cautiously with ephedrine medication in digitalized patients.

Quinidine. The circumstances under which digitalis may be combined with quinidine are described under the use of the latter drug in auricular fibrillation.

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CHAPTER 29

QUINIDINE

History. Quinidine, an optical isomer of quinine, is one of the natural alkaloids found in cinchona bark. It was first described in 1848 by van Heyningen and was prepared and given its present name by Pasteur in 1853. Both quinine and quinidine are used for the treatment of malaria and it was noted a number of years ago that malarial patients who also had auricular fibrillation would occasionally be cured of arrhythmia by these drugs.

Wenckebach (1914) reported on the use of quinine alkaloids in certain cardiac arrhythmias. He relates the following experience (cited by Beckman, 1934): "In 1912, a patient presented himself in my office wishing to get rid of his attacks of auricular fibrillation. He knew that this was the so-called perpetual or complete arrhythmia and that his attacks ceased for the most part spontaneously after from two to fourteen days. He was a stout man, aged about fifty, able to do a good deal of bodily exercise and even during the attack to walk for four or five hours. From this fact it was clear that the efficiency of his heart and circulation was only slightly diminished by the attack. He did not feel great discomfort during the attack but, as he said, being a Dutch merchant, used to good order in his affairs, he would like to have good order in his heart business also and asked why there were heart specialists if they could not abolish this very disagreeable phenomenon. On my telling him that I could promise him nothing, he told me that he knew himself how to get rid of his attacks, and as I did not believe him he promised to come back the next morning with a regular pulse, and he did. It happens that quinine in many countries, especially in countries where there is a good deal of malaria, is a sort of drug for everything, just as one takes acetylsalicylic acid today if one does not feel well or is afraid of having taken cold. Occasionally, taking the drug during an attack of fibrillation, the patient found that the attack was stopped within from twenty to twenty-five minutes, and later he found that a gram of quinine regularly abolished his irregularity.

"I was greatly struck by this fact, and afterward tried this sort of treatment in many cases of auricular fibrillation. My success was disappointing, in that quinine abolished auricular fibrillation in only a few cases and in those cases only when the onset of this form was quite recent, never when it was of several years' duration. At the same time, I found that even in those cases in which auricular fibrillation was not abolished, the drug had a marked soothing action on the often terrific rate of the ventricle."

Frey (1918), impressed by the report of Wenckebach, studied quinine, cinchonine and quinidine in patients with auricular fibrillation and found quinidine to be the most effective.

Relative Importance of Quinidine. For every patient receiving quinidine for auricular fibrillation, at least a score are given digitalis. Nevertheless, when quinidine is used, it must be employed with a great deal of knowledge, for it is a dangerous as well as an effective drug. Therefore, quinidine will be discussed at length and this in turn offers an opportunity for correlating the physiology of auricular fibrillation with the pharmacodynamics of certain cardiac drugs.

Chemistry. Quinidine is the dextro-isomer of quinine and occurs with the latter in cinchona bark. The chemistry of the cinchona alkaloids is presented under quinine.

Comparison with Quinine. Quinidine shares many of the pharmacological properties of quinine. It is a "general protoplasmic poison" but is somewhat less toxic to unicellular organisms. Nevertheless, it has approximately the same antimalarial action as quinine, and is occasionally used in malaria when idiosyncrasy prevents the employment of quinine. Quinidine also has antipyretic and oxytocic actions. It is believed to be more toxic for man than quinine. This may be due in part to the fact that quinidine is employed in conditions the nature of which exaggerates the toxicity of the drug.

Both alkaloids are depressant to skeletal and cardiac muscle. The refractory phase is prolonged and the contractility is diminished. In comparison with quinine, quinidine affects the refractory period of cardiac muscle more than it affects the contractility. Therefore, quinidine is the cinchona alkaloid of choice in the treatment of auricular fibrillation.

Absorption and Excretion. Quinidine sulfate, the preparation usually employed, is readily absorbed from the intestinal tract. The major part is quickly excreted in the urine (Figure 56), mainly unchanged.

Pharmacological Actions. As has been stated, quinidine is a general protoplasmic poison similar to quinine. This action is due, at least in part, to a ferment-inhibiting property common to the quinine alkaloids. This inhibition extends to many enzymatic processes. It finds particular expression in the effect of quinidine on muscle, both skeletal and cardiac.

Skeletal Muscle. The action of quinidine on skeletal muscle is qualitatively similar to that of quinine and is described elsewhere (page 908).

Cardiac Muscle. The action of quinidine on the heart is the basis for its only therapeutic use other than for malaria. Therapeutic doses of quinidine produce changes in the heart which can be summarized as follows:

(1) *The refractory period* is increased, often as much as 50 to 100 per cent. Appreciation of the fact that quinidine prolongs the refractory period of the heart muscle is essential to an understanding of its cardiac action.

(2) *The myocardial excitability* is decreased, mainly due to the increased refractory period. Auricles and ventricles are affected in the same manner. This property of quinidine makes it of value in treatment of premature systoles.

(3) *The rate of the heart* is altered. If the rhythm is regular, the heart rate may be slowed. The slowing is not vagal in origin because it occurs after full atropinization. Indeed, some believe that the peripheral vagal mechanism is mildly paralyzed by quinidine. The bradycardia results from the action of the drug on the refractory period of the sinoauricular node where it decreases the rate of impulse formation. Large doses may even cause diastolic arrest.

(4) *The amplitude of contraction* of the compensated heart may be increased considerably by moderate doses of the alkaloid. This is due to the slower rate resulting in increased diastolic filling of the ventricles. Here again, the effect on amplitude is due to the increase in refractory period. With toxic doses or in heart failure, however, the cardiac excursion is not increased by quinidine and may be decreased, due to the depression of muscular contractility.

(5) *The conduction* of impulses in heart muscle is slowed by quinidine. The conduction between auricle and ventricle is retarded and various degrees of A-V

block may appear after large doses. Atropine does not alter this block. It is the slowing of auricular conduction, as described later, which tends in some cases to fix and perpetuate the circus movement of auricular fibrillation.

Auricular Fibrillation. Auricular fibrillation, by far the most common of all the permanent heart arrhythmias, is the disorder in which quinidine has unique value. In order to understand clearly the action and use of quinidine in auricular fibrillation, a brief description of the nature of the pathological physiology of this arrhythmia is necessary.

Clinically, there are two types of auricular fibrillation, the paroxysmal and the chronic. The paroxysmal form is usually associated with acute infections, hyperthyroidism, marked physical exertion, the use of alcohol, tobacco, anesthesia, epinephrine, etc. Its etiology may elude investigation. The chronic form of the disorder, which is the more common, usually results from permanent auricular strain. The chief physiological cause is increased intra-auricular pressure, and the chief clinical occurrence is in congestive heart failure. Occasionally, there is no detectable heart disease. Careful pathological examination of the auricles of patients who during life had long-standing auricular fibrillation reveals no unique or characteristic lesions that can be considered responsible for the onset or continuation of the arrhythmia.

Pathological Physiology of Auricular Fibrillation. Auricular fibrillation is a disorder of cardiac function due to alterations in conduction in auricular muscle and to changes in refractory period. These result in the replacement of orderly auricular contractions by a self-perpetuating circus movement composed of a central path about the origin of the great veins and collateral waves issuing from this parent path.

The *auricles,* for all practical purposes, are in "functional" diastole. They are markedly engorged and show rapid ineffectual fibrillary twitchings at the rate of 450 or more per minute (Figure 57).

The *ventricles,* fortunately, cannot respond to all these many impulses arising from the circus movement of the auricle, due in part to various degrees of auriculoventricular block, and to the refractory state of the ventricular muscle when many of these impulses arrive. The ventricular rate is usually 120 beats or more per minute. Characteristically, the ventricular contractions are totally irregular in force, rate and rhythm. A *pulse deficit* exists due to the inability of some ventricular systoles to raise the aortic valve leaflets. This is caused by the poor diastolic filling of the ventricles, due in turn to the irregular and rapid rate of contraction. The ventricular rate may be one and one-half times the pulse rate.

Auricular fibrillation is closely related to *auricular flutter* and *paroxysmal tachycardia.* Some believe that auricular flutter has a single and constant path for the circus movement, whereas auricular fibrillation has one major path and several vagarious collateral circuits.

Mechanism of Circus Movements in Muscle Rings and Application to Auricular Fibrillation. The basic abnormality of auricular fibrillation or flutter is a circus movement and it is therefore necessary to understand how such a movement originates and perpetuates itself, and how it may be stopped.

In 1908, Mayer experimented on circular strips of muscle from the umbrella of the jellyfish, and found that if a ring of muscle is stimulated so that the impulse travels only in one direction, a circus movement is established and may continue for many minutes or hours. Garrey (1914) and Mines (1914) showed that the same principles which underlie these simpler experiments applied also to auricular fibrillation. In order to establish a circus movement, the following conditions are necessary: (1) An area of muscle refractoriness must exist so that the wave of contraction can progress only in one direction and along one path. (2) This original refractory area must have recovered by the time the excitation process reaches it again, so that an "excitable gap" of tissue always exists. These facts are made evident in Figure 55 which represents simple circular muscle strips.

The main conditions, as outlined by Lewis, which tend to alter the excitable gap and hence the circus movement are shown in the following table:

Abolish gap and stop circus movement	*Increase gap and perpetuate circus movement*
1. Quicker conduction	1. Slower conduction
2. Longer refractory period	2. Shorter refractory period
3. Shorter path	3. Longer path

It is evident that the circuit time of the circus movement, that is, the time it takes to make one complete revolution, must always be greater than the refractory period of the muscle. A slowing of conduction naturally increases and a speeding of conduction decreases the circuit time.

These principles may more clearly be understood by an analysis of the following example. Suppose that the circumference of the muscular ring (depicted in Figure 55, C and D) undergoing the circus movement is 100 mm and that the contraction wave travels 500 mm per second. Then each circuit is made in 0.2 second. Now assume that the refractory period is 0.15 second; then any one point on the muscle ring recovers from its contraction when the next impulse is 0.05 second or 25 mm distant. Therefore, a 25 mm portion of the muscle ring will again be ready to contract and this represents the "excitable gap."

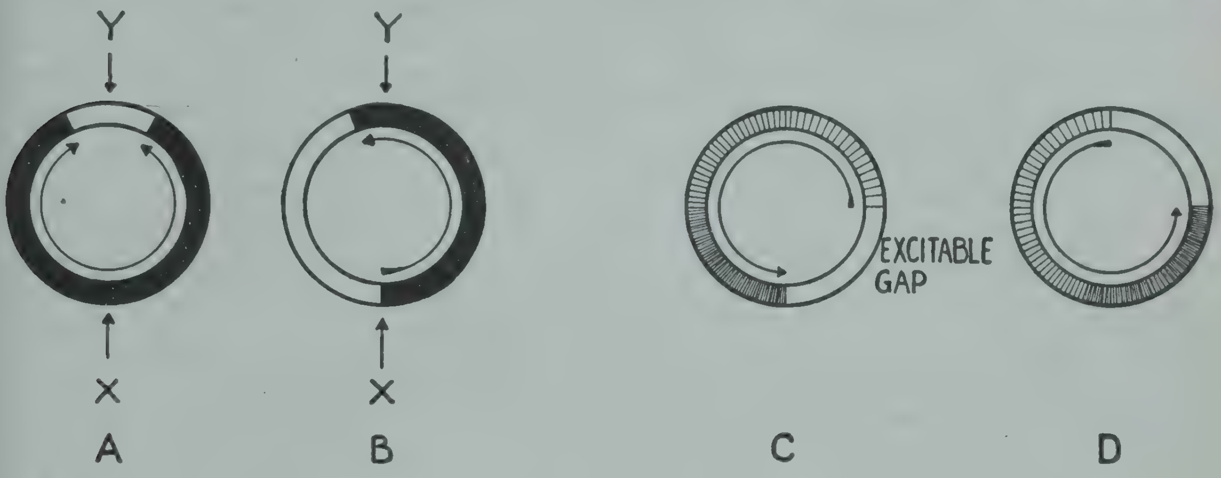

Figure 55. *Mechanism of circus movement.*

Solid black indicates refractory muscle; unshaded area signifies excitable muscle. Curved arrows show direction of contraction waves. *A.* If a stimulus is applied at point X to a circular strip of muscle, a wave of contraction is initiated which passes in both directions. When point *Y* is reached, the waves of contraction cease because the areas contiguous to *Y* are still refractory from having just contracted. *B.* If the wave of contraction can pass in only one direction from point *X*, it will make a complete circuit along the strip of muscle. If by the time point *X* is again reached this region has recovered its excitability, the circus movement will continue to travel the muscular circuit over and over again. *C.* The unshaded portion represents the excitable gap, that is, the area of muscle which has recovered from the previous wave of contraction. An excitable gap must always be present or the circus movement is automatically blocked. The intensity of shading indicates the degree of refractoriness of that portion of the ring of muscle which has not yet recovered from the wave of contraction. The head of the circular arrow shows the advancing margin of the contraction wave. *D.* Same ring of muscle as shown in *C,* but depicted a fraction of a second later.

If conduction is slower, the impulse arrives later and the muscle has even more time to regain excitability. The circus movement is perpetuated in this manner. If the refractory period is increased, it takes longer for the muscle to recover, and the impulse now finds the tissue inexcitable. In this way, the circus movement is blocked. In the example given, the circus movement could be stopped either by lengthening the refractory period from 0.15 second to 0.20 second, or by increasing the rate of conduction to 670 mm per second.

This information may now be applied to clinical auricular fibrillation. The normal rate of impulse conduction in auricular muscle is 1000 mm per second, but in the fibrillating auricle this rate is reduced to 500 mm per second. The refractory period of normal auricular muscle is about 0.20 second in duration, with cardiac rates up to 100 beats per minute; but, if the auricle is fibrillating, this refractory period is reduced to about 0.10 second. The data available are presented in Table 31 (modified from Wright, 1936).

Inspection of the data in Table 31 indicates that a therapeutic agent can effectively block the circus movement either by increasing the refractory period or by increasing the speed of conduction. Unfortunately, there is no drug known which accomplishes both of these feats, because it is physiologically impossible to stimulate heart muscle in respect to one function (increased speed of conduction) and at the same time depress the heart in regard to another function (prolonged period of refractoriness).

Quinidine Action in Auricular Fibrillation. Quinidine acts in auricular fibrillation by increasing the refractory period of the auricular muscle. When the circus movement finds refractory tissue in its path, it comes to an end. As Osler phrased it, "The head of the circulating wave catches up with its tail." An increasing number of circulating impulses in the auricle are blocked when they find the auricular muscle inexcitable. Finally, they all die out and the auricle becomes quiescent. In this quiescent interval, the sinoauricular node once again resumes dominance and initiates normal rhythm. Occasionally, however, in the period during which the number of fibrillary twitchings are gradually diminishing, auricular flutter may intervene. This flutter may cause a marked increase in ventricular rate, which may be dangerous to the patient (Figures 56 and 57).

TABLE 31

DATA ON CIRCUS MOVEMENTS
OF AURICULAR FIBRILLATION AND FLUTTER
(After Wright, 1936.)

AURICULAR FIBRILLATION

Rate of auricular contractions	450 circuits per min.
Circuit time of each circus movement	0.13 second
Refractory period of auricle	0.09 second
Rate of conduction	500 mm per second
Length of path (circumference)	65 mm (0.13 x 500)
* Size of excitable gap	20 mm ($\frac{4}{13}$ x 65)

AURICULAR FLUTTER

Rate of auricular contractions	350 circuits per min.
Circuit time of each circus movement	0.17 second
Refractory period of auricle	0.11 second
Rate of conduction	500 mm per second
Length of path (circumference)	85 mm (0.17 x 500)
Size of excitable gap	30 mm ($\frac{6}{17}$ x 85)

* Because most of auricular muscle has a refractory period almost equal to the circuit time and not 0.04 of a second less, as given in the table, the excitable gap is not 20 mm but actually very small, so small indeed that the "crest of one wave rides close to and interlaces with the wake of the previous wave."

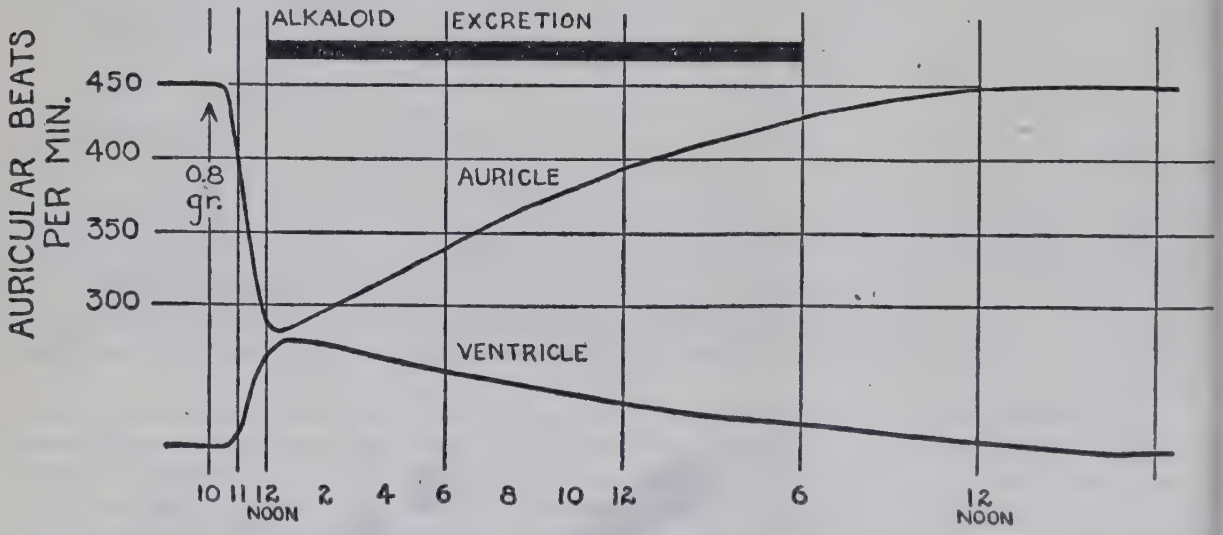

FIGURE 56. *The effect of a single 0.8 gram oral dose of quinidine on the auricular and ventricular rates in a patient with auricular fibrillation.*

The solid black line represents the period during which quinidine could be detected in the urine. Note that the peak effect of the drug on the heart occurs within two to three hours after administration, following which there is a gradual return to the original rates. Observe how closely the rise in ventricular rate mirrors the fall in auricular rate. Compare with Figure 57. (After Lewis, 1934. Courtesy of Shaw and Sons.)

This is because the ventricle responds to more auricular impulses as the auricular rate slows from one of fibrillation to flutter, especially if an A-V block of 2:1 grade intervenes. For example, a ventricular rate of 110 beats per minute may increase to 160, if quinidine causes a stage of auricular flutter with an auricular rate of 320 beats per minute.

Quinidine sometimes fails to stop auricular circus movement. This is because the drug also slows conduction in auricular muscle, and consequently each circus movement requires a longer time to complete its circuit. The muscle now has more chance to recover from its previous contraction and the arrhythmia may be perpetuated. If the action on the refractory period is greater, quinidine tends to stop the fibrillation. If the action to slow conduction is greater, quinidine tends to fix and perpetuate the fibrillation. The latter effect accounts for many failures in quinidine therapy.

Comparison of Quinidine and Digitalis in Auricular Fibrillation. Quinidine is used to cure auricular fibrillation by restoring normal sinus rhythm. Digitalis, on the contrary, does not cure auricular fibrillation. Under its influence the ventricles beat more slowly, more regularly and more efficiently. This is accomplished especially by the direct cardiotonic muscular action of digitalis, and also to some extent by its effects on the conduction of impulses from auricle to ventricle.

Both drugs produce longer refractory periods and slower conduction, but by very different mechanisms—digitalis by increasing the force of the myocardial contraction, and quinidine by depressing the restorative metabolism of muscle. The question is legitimately raised as to why digitalis does not cure auricular fibrillation. The answer to this is fully discussed on page 532.

Toxic Reactions. Not all the toxic reactions to quinidine occur as a result of the drug itself and some are due to the nature of the disorders for which quinidine is used.

Cinchonism. Quinidine, like most cinchona alkaloids, can cause the syndrome known as "cinchonism." This is fully described on page 910. Severe cinchonism, however, is fairly infrequent after quinidine.

Idiosyncrasy. Idiosyncrasy to quinidine is not rare and must be carefully tested for in each patient. The reaction consists of respiratory distress, occasionally with temporary cessation of respiration, cyanosis, dizziness, nausea and vomiting, and cold sweat.

Embolism. The appendages of auricles which have been fibrillating for months often contain more or less firmly attached mural thrombi. The sudden reversion to a normal rhythm produced by quinidine, with the resultant strong and complete contractions of the auricles, may cause these thrombi to be dislodged and to produce embolic occlusion of important vessels. Death may result. The attitude toward embolism caused by quinidine is changing and it is now believed that this danger has been overemphasized. Accidents of this sort are said by some to be no more frequent with quinidine therapy than with digitalis or no medication whatsoever.

Dangerous Tachycardia. As explained previously, when quinidine slows the rate of the fibrillating auricles to a point where the ventricles respond to more stimuli, that is, when auricular flutter replaces auricular fibrillation, there occurs a sudden marked tachycardia which may be serious (Figures 56 and 57). This can be largely prevented by previous digitalization of the patient.

Ventricular Standstill. Quinidine depresses the S-A and A-V nodes, and in the short period of auricular quiescence immediately after the cessation of the auricular circus movement, the pacemaker of the heart may not speedily resume its function. This may prove fatal.

Ventricular Fibrillation. Death from ventricular fibrillation after quinidine occurs more commonly than is usually stated, and many fatalities formerly attributed to embolism were probably due to ventricular fibrillation. This has been proved by electrocardiograms fortuitously taken immediately before death. That ventricular fibrillation can be produced by a myocardial depressant such as quinidine emphasizes the fact that this fatal arrhythmia can be caused by depressants as well as by stimulants.

Contraindications to Quinidine Therapy. There are many contraindications to the use of quinidine. Patients who develop severe cinchonism or have an idiosyncrasy to the drug should not receive it. Quinidine should not be used in the presence of acute infections or for patients with bacterial endocarditis. Severe cardiac failure or marked cardiac damage without failure (*e.g.,* coronary thrombosis) also limits its use. It should not be employed in patients with long-standing valvular disease or auricular fibrillation. Aged patients or those with marked cardiac enlargement or hypertrophy must be given quinidine cautiously if at all. Hyperthyroid patients with auricular fibrillation should not receive quinidine until after thyroid resection. A patient with angina pectoris whose pain was relieved by the onset of auricular fibrillation should not receive quinidine to revert his rhythm to normal. One who presents a history of embolic episodes cannot safely be treated with the alkaloid. Lastly, if complete heart block exists, there is nothing gained by attempting to restore normal auricular rhythm.

Many of the above contraindications are not absolute, and each case is a law unto itself. For example, auricular fibrillation of ten years' duration has been reverted to normal by means of quinidine. Furthermore, in certain hopeless cases of severe heart failure in which all other therapy has failed, quinidine may be used in spite of contraindications, and may occasionally stop the arrhythmia with beneficial results (Kohn and Levine, 1935). One may summarize the contraindications to quinidine by stating that the drug is not usually used (1) when there exist acute infective or toxic processes in the body; (2) if the heart is seriously damaged or in failure; (3) when the use of the drug is likely to cause a serious accident, such as embolism or idiosyncrasy, or (4) if the return to regular sinus rhythm is unlikely or not particularly desirable.

Indications for Use of Quinidine in Auricular Fibrillation. The best results from the use of quinidine are obtained in (1) young patients exhibiting little cardiac damage and in whom the arrhythmia is of recent origin; (2) cases of persistent auricular fibrillation after thyroidectomy, where results are truly brilliant; and (3) patients whose disorder causes intractable palpitation and whose chief complaint, even though they are digitalized, is a tumultuous beating of their hearts. In addition, as was stated, the drug is perhaps indicated where all other therapy has failed. In some clinics, quinidine is used as a prophylactic measure to prevent the onset of auricular fibrillation in cases of rheumatic mitral stenosis with frequent auricular extrasystoles presaging the onset of the arrhythmia. In small doses, the drug often causes the disappearance of these premature beats and perhaps delays the onset of auricular fibrillation.

Preparations. The official U.S.P. and B.P. preparation and the one commonly employed is *Quinidine Sulfate.* It consists of fine needle-like crystals which are odorless, very bitter to the taste and darken on exposure to light. *Quinidine,* N.N.R., the alkaloidal base, is also available.

Therapeutic Uses of Quinidine. *Auricular Fibrillation.* The patient with this type of arrhythmia who is to receive quinidine should be under close medical observation, preferably in the hospital. Two or three days of complete rest in bed with mild sedation should precede quinidine therapy. If the ventricular rate is above 90 beats per minute, the patient should be digitalized to lower this rate. Digitalis will also prevent ventricular tachycardia from occurring after quinidine

Technic. There are many different methods of administering quinidine, but the following is perhaps as safe and effective as any. A test dose of 0.2 or 0.3 gram of quinidine sulfate is given the day before therapy is started and the patient is carefully observed for symptoms of idiosyncrasy or cinchonism. The following day, 0.4 gram is administered every four hours, five times daily, starting at 8:00 A.M. This schedule is continued for seven to 10 days and comprises a "course" of quinidine.

One discontinues the drug if toxic signs or symptoms occur, if a tachycardia of over 125 beats per minute develops, or if obstinate auricular flutter appears. One also stops the drug upon the advent of showers of petechiae, which may signify the imminence of embolism, and premature ventricular systoles, which may presage ventricular fibrillation.

A second course of quinidine may be given after two or more weeks of rest if the first course was unsuccessful. The dosage system may now be altered. Digitalization should probably be instituted before quinidine is used a second time. The digitalis is usually stopped when the quinidine is started. A third and even a fourth course of quinidine may be given, with intervals of a month between trials. If still unsuccessful, the further use of quinidine is probably futile.

After normal cardiac rhythm is established, one gives 0.2 to 0.3 gram of the drug three times a day for one or two weeks. The dose is then gradually reduced over a period of several weeks. The daily maintenance dose varies greatly for each patient but is usually between 0.2 and 0.6 gram. In a few cases, no maintenance dose is necessary. This is particularly true in thyrotoxic patients after thyroidectomy. If auricular fibrillation recurs, courses of quinidine may be resumed but the time eventually comes when further attempts are unsuccessful.

Success in restoring normal rhythm by using quinidine depends upon the careful selection of cases and the proper dosage of the drug. About 65 to 80 per cent of all *properly selected and treated* cases can be reverted to a normal sinus rhythm (Stroud and Laplace, 1935; Fahr, 1938) (Figure 57). Unfortunately, in a number of these cases fibrillation may occur again within a few months. It is possible that this is due to a failure on the part of some of the patients faithfully to continue their daily maintenance dose. Fahr (1938) reports that quinidine therapy was successful in approximately 65 per cent of more than 500 patients with auricular fibrillation and that in nearly every case the arrhythmia did not recur if the daily prophylactic dose was taken. These results are considerably better than those reported by others. Some authorities maintain there is no good evidence that in the long run quinidine materially reduces mortality or prolongs life. Nor is it apparent that the chronic fibrillating heart, when adequately digitalized, is any less efficient than the heart restored to a normal sinus rhythm by quinidine. Nevertheless, some properly digitalized patients who are uncomfortable and restricted in their ability to perform physical exertion can be restored to a fairly active life after the auricular fibrillation has been abolished by quinidine therapy.

Before using quinidine, the physician must weigh the possible benefits to be derived against the possible dangers incident to the use of the drug. In some cases, such as in post-thyroidectomy patients in whom auricular fibrillation persists or in young persons with good heart muscle and fibrillation of short duration, there is no doubt that quinidine should be employed.

Auricular Flutter. Quinidine is indicated in this disorder but it is less effective in restoring auricular flutter to a normal rhythm than in cases of auricular fibrillation. It is possible that in auricular flutter the action of quinidine may be relatively greater on the conduction time of auricular muscle than on the refractory phase, which would tend to perpetuate the flutter and militate against success in reverting the rhythm to normal. Some cardiologists reserve quinidine therapy for those patients who fail to respond to digitalis.

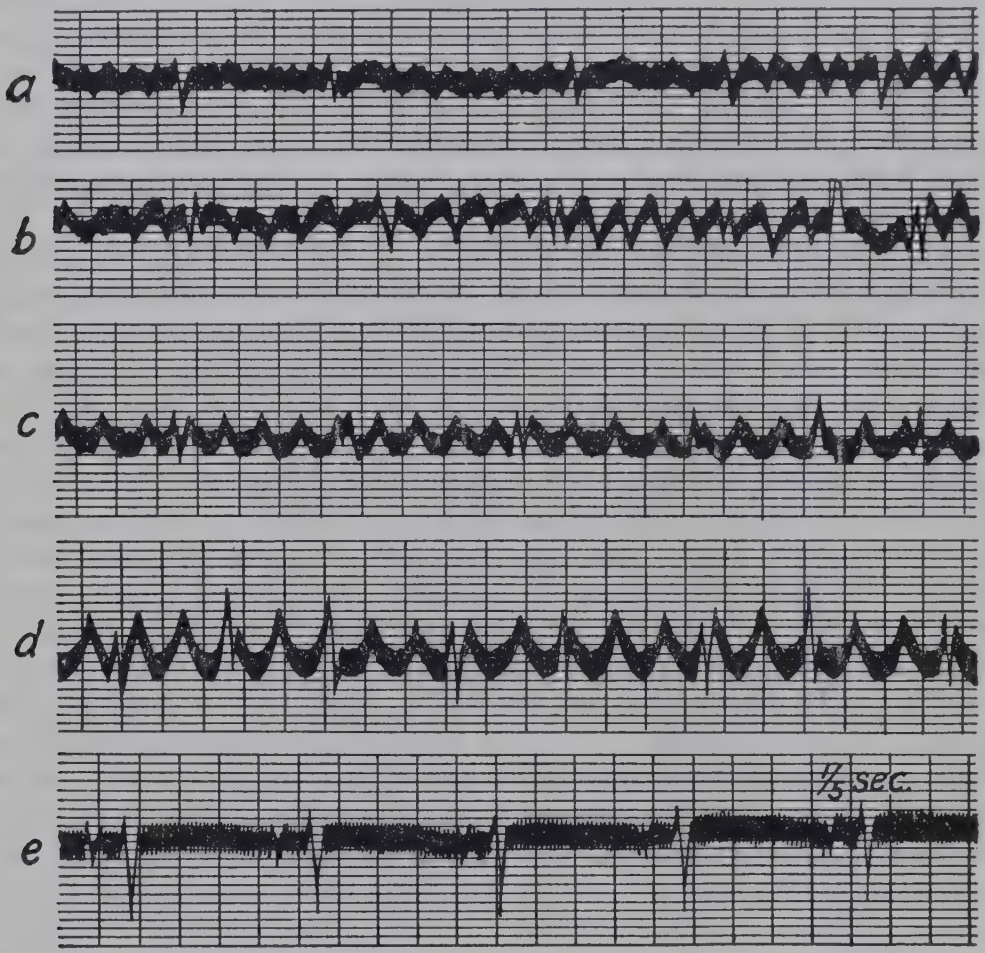

FIGURE 57. *Electrocardiographic changes noted during quinidine therapy of auricular fibrillation.*

Time in fifths of a second. (*a*) Before treatment: auricular rate of 450 beats per minute. (*b*) After one dose (0.3 gram) of quinidine: the auricular rate has fallen to 350. (*c*) At end of first day's treatment (after one gram of quinidine): the auricular rate has fallen to 296. (*d*) At the end of the second day's treatment (after two grams of quinidine): the auricular rate has fallen to 247, and the oscillations have become almost regular as in auricular flutter. Note the increase in ventricular rate. (*e*) Sixteen hours after the previous tracing (after 2.3 grams of quinidine): normal sinus rhythm has been restored. (After Lewis, 1937. Courtesy of Shaw and Sons.)

Paroxysmal Tachycardia. In paroxysmal tachycardia of *auricular or junctional origin,* quinidine probably acts by depressing the S-A node or an extranodal focus for the abnormal rhythm. The hearts of patients with this malady are usually in better condition than those with auricular fibrillation. Consequently the contraindications to quinidine are fewer and the dose is smaller, 0.3 gram being given three times a day, either to relieve or prevent paroxysms. For other therapy of this disorder, the index should be consulted.

In paroxysmal tachycardia of *ventricular origin,* quinidine may be effective in stopping as well as in preventing attacks (Fahr, 1938), and at times its action is dramatic and life-saving. The danger exists, however, that the drug may produce ventricular fibrillation in such cases.

Extrasystoles. Many measures are available if therapy is required for this disorder. Quinidine may be used to afford relief and acts by decreasing the muscular irritability which may be the basis for the extrasystoles. It can be employed in doses of 0.3 gram, two or three times a day. The drug is helpful in tiding a patient over a period of disagreeable cardiac consciousness, but he often stops the treatment voluntarily because it is more troublesome than the disability. The reassurance he obtains from the discovery that something can be done for him is nevertheless important.

Coronary Occlusion. Quinidine has been suggested for routine use in cases of coronary thrombosis to reduce muscular irritability and lessen the incidence of ventricular tachycardia or fibrillation. Ventricular fibrillation, however, is no longer considered a frequent cause of death in coronary occlusion. Furthermore, quinidine is a toxic drug, may in itself cause ventricular fibrillation, and should not be used for prophylactic purposes in patients with fresh myocardial damage.

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CHAPTER 30

THE NITRITES

History. Glyceryl trinitrate was discovered by Sobrero in 1847. Amyl nitrite was first used in medicine by Guthrie in 1859. Both compounds were introduced in the 1860's for the treatment of angina pectoris, independently by Richardson and Brunton. The latter reported his work in 1867 and also described his experiences with amyl nitrite in his well-known textbook published many years later (1897), where he wrote as follows:

> "This drug (*amyl nitrite*) when inhaled causes very rapid dilatation of the vessels indeed, with flushing of the face, a feeling of fulness in the head, and a very great fall of the blood pressure. On account of this fall of blood pressure, it eases the heart at once when this organ is unable to overcome the resistance which is opposed to it. . . . When the heart contracts against a resistance which it cannot overcome, the pain in the heart . . . becomes great. You can readily see that the excess of work to be done over power to do it, which causes the pain in these cases, may depend upon the fact either that the peripheral resistance in the vessels has been increased above the normal, or that the power of the heart to overcome the resistance has been lessened below the normal. In either case, the resistance becomes too great for the heart. In cases of angina pectoris, this condition appears to obtain, and there you frequently find that there are both conditions to deal with, *viz.,* a heart which has become enfeebled and a resistance which has become increased above the normal.
>
> "Many years ago, when I was a resident physician, I had a case of angina pectoris under my care. I used to go at all hours of the day and night and take tracings of the man's pulse. I found that during the attack of angina pectoris the pulse became very hard indeed, and the oscillations became very small. He had a certain amount of aortic regurgitation, and his normal pulse wave was very large. As the man's pain came on, the pulse became smaller and quicker, and when the pain was excessive the pulse became very rapid, but hardly perceptible. Now, it is almost impossible to explain such a change in the pulse as we have here without assuming that the peripheral arterioles had become enormously contracted. It therefore occurred to me that if one were able to dilate the arterioles the man's pain ought to subside. I knew that nitrite of amyl had the effect of dilating the vessels, and I tried it, with the result that no sooner had the flushing of the face occurred, and the vessels begun to dilate, than the pain disappeared. Since that time nitrite of amyl has become recognised as a regular remedy for the paroxyms of angina pectoris."

It is obvious that Brunton thought that anginal pain was due to paroxysmal increases in blood pressure, and that the relief afforded by amyl nitrite was due to the lowering of blood pressure. It is now known that the cardiac pain in patients with angina pectoris is due to myocardial anoxia as a result of coronary artery disease, and that pain occurs when there is a discrepancy between the myocardial demand for oxygen and the supply brought by the coronary circulation (*see* Lewis, 1932; Hamman, 1935). If the blood pressure rises with the attack of pain, it is incidental to the pain and not the cause (Figure 61). It is thus clear that amyl nitrite was introduced for the treatment of the anginal syndrome on a false assumption as to the mechanisms involved, illustrating that the clinical efficacy of a particular therapy is no proof of the theory underlying that therapy.

Chemistry and Classification. The compounds of the nitrite group include both nitrites and nitrates, and may be listed as in Table 32.

Relation Between Chemistry and Action. The term "nitrite" is used in the following discussion to include both nitrites and nitrates. This is permissible on the ground that all the compounds listed depend for their action upon the liberation of the nitrite ion (NO_2) in the body. Both organic and inorganic nitrites readily release the nitrite ion and it is relatively immaterial whether an organic radicle or a metal serves as the carrier. Only the organic nitrates, however, readily release the nitrite ion in the body. Thus potassium nitrate in large doses can be taken as a diuretic without causing appreciable nitrite action. Bismuth subnitrate, the only inorganic nitrate used for a nitrite action, undergoes reduction in the colon to nitrite due to the effect of bacteria. The nitrite ion thus liberated is absorbed into the blood stream and exerts its characteristic actions. In this connection it is of interest to note that after ingestion of nitrate, nitrite may be found in the urine only if an *E. coli* infection of the urinary tract exists.

TABLE 32

CLASSIFICATION OF THE NITRITES

INORGANIC	Sodium Nitrite	$NaNO_2$
	Bismuth Subnitrate	$BiONO_3$
ORGANIC	Amyl Nitrite	$C_5H_{11}NO_2$
	Ethyl Nitrite (Nitrous ether)	$C_2H_5NO_2$
	Glyceryl Trinitrate (Nitroglycerin; glonoin)	$C_3H_5(NO_3)_3$
	Erythrityl Tetranitrate	$C_4H_6(NO_3)_4$
	Mannitol Hexanitrate	$C_6H_8(NO_3)_6$

The organic nitrates such as nitroglycerin are partially decomposed in alkaline media to nitrites, and this is probably the mechanism operative in the organism. It is unexplained, however, why nitroglycerin is therapeutically active in doses only $\frac{1}{100}$ that of sodium nitrite, if it is necessary for the nitrate to be changed to nitrite. It is likely that the inorganic nitrites are largely decomposed in the gastro-intestinal tract before absorption, and must therefore be given in large doses. Nitroglycerin, on the other hand, is readily absorbed and is not decomposed until it reaches the tissues. It has also been suggested, but never proved, that organic nitrates diffuse more readily into cells than do nitrites and are changed to nitrite within the cell.

Newer Nitrites. A number of aliphatic nitrites and nitrates have been studied experimentally in an attempt to find therapeutically useful volatile agents superior to amyl nitrite (Krantz and associates, 1938, 1939). One of these, *octyl nitrite* (2 ethyl-n-hexyl-1-nitrite) has a much longer duration of vasodepressor action than amyl nitrite and apparently is less toxic. Krantz and coworkers (1939) have also studied, both experimentally and clinically, the actions of *isomannide dinitrate,* a crystalline substance which has a longer duration of hypotensive effect than either erythrityl tetranitrate or mannitol hexanitrate. Considerably more clinical investigation is required to establish the ultimate therapeutic value of these newer nitrites.

Pharmacological Actions

The basic action of the nitrite ion in the body is to relax smooth muscles, especially those of the finer blood vessels. Therefore, a fall in blood pressure is the most characteristic pharmacodynamic effect of the drug. Actions other than the antispasmodic are relatively unimportant except from the standpoint of toxic side-effects.

The antispasmodic action of nitrites on the smooth muscles of blood vessels and other organs is independent of innervation. The drug acts on smooth muscles without decrement after destruction of the cerebrospinal axis, as well as on peripherally denervated structures, excised organs and isolated arterial rings. Nor is the vasodilator action blocked by atropine. Muscles relaxed by nitrites are not paralyzed and muscular stimulants and constrictor nerve impulses can still exert their characteristic motor effects. Tone of smooth muscle is reduced by nitrites, but the ability to contract maximally in response to adequate stimulation remains unimpaired.

Cardiovascular Actions. The most prominent and important action of nitrites is to dilate the smaller blood vessels. These include arterioles, capillaries and venules, but the effect is more marked on the postarteriolar vascular bed. The rate of capillary blood flow is increased. Lueth and Hanks (1938), for example, noted a definite increase in the rate of blood flow through the capillaries of the nailfold in patients receiving as little as 0.2 mgm of nitroglycerin. The larger veins and arteries are also relaxed to some extent. Dilatation of fairly large systemic arteries is suggested by the relaxation noted in the radial and temporal arteries after medication with nitrites, the pulse becoming more bounding even when there is no change in the stroke volume output of the heart or in the diastolic pressure (Weiss and Ellis, 1933). Oscillometric measurements also indicate the increase of pulse volume which occurs after nitrites.

Responses of Different Vascular Beds. The intensity of action of nitrites varies in the different vascular beds of the body. The postarteriolar vessels—capillaries and venules—are most susceptible to nitrites (Weiss, Wilkins and Haynes, 1937) and this is the basis for the peripheral circulatory collapse which can be induced by the drug.

Skin Vessels. Cutaneous vasodilatation is seen especially after the inhalation of amyl nitrite which produces a deep blush of the face, neck and clavicular area (blushing zone). The skin is hot and dry and the surface temperature rises. Occasionally the flush may extend to involve the skin of the trunk, but seems not to extend below the umbilical region. Cutaneous vasodilatation can result from a dose of amyl nitrite causing no fall in blood pressure. Although other amyl compounds, such as amyl chloride, cause flushing, this occurs only after large doses and the nitrite radicle therefore appears to be responsible for the action. When the slower-acting nitrites are administered, however, no flush is noted. For example, sodium nitrite in doses of 0.2 to 0.3 gram does not dilate the cutaneous capillaries and venules and in this respect the drug differs sharply from other vasodilators such as histamine or acetylcholine (Weiss and Ellis, 1933).

Meningeal Vessels. The smaller vessels of the meninges are widened by nitrites, as can be observed through cranial windows. This is the basis for the rise in intracranial pressure and for the pulsating transitory headache which is noted by many persons after nitrite administration. Headache is especially likely to occur after the inhalation of amyl nitrite, and a protracted and often intense cephalalgia may result from erythrityl tetranitrate.

Splanchnic Vessels. Plethysmographic studies of abdominal viscera indicate that nitrites increase organ volume and enhance venous return, findings consistent with the occurrence of dilatation of the smaller blood vessels. It is usually stated that the main site of action of nitrites is on the splanchnic arterioles. Marked falls in diastolic blood pressure are rarely seen in patients after nitrites, however, as would be expected if the drug caused extensive arteriolar dilatation in the splanchnic bed, because changes in diastolic pressure usually signify alterations in the arteriolar resistance. Even when circulatory collapse occurs from susceptibility to nitrites or from overdosage, postarteriolar rather than arteriolar dilatation is the cause, and indeed the arterioles may be constricted due to compensatory vasomotor reflexes (Wilkins, Weiss and Haynes, 1938).

Coronary Vessels. Nitrites relax the coronary vascular tree, the basis for the chief therapeutic use of nitrites in the relief of the pain of angina pectoris. Coronary vasodilatation is said to outlast the effect of nitrites on other vascular beds. Coronary blood flow is increased despite the concomitant fall in aortic blood pressure. This fact has been amply confirmed by many investigators since the early experiments of François-Franck (1903) and Schloss (1913) (*see* Katz and coworkers, 1938; Boyer and associates, 1939; Essex and collaborators, 1940). For example, Essex and collaborators (1940), employing the technic of thermostromuhr units implanted on the coronary arteries of trained unanesthetized dogs, demonstrated that nitroglycerin enhanced coronary blood flow by 30 to 100 per cent. Arteriosclerotic coronary arteries are not greatly affected by nitrites but healthy collateral branches may be dilated. This possibility is supported by the experimental observations of Smith (1921) who ligated the left coronary artery in dogs and noted that nitroglycerin then caused a partial or complete disappearance of myocardial cyanosis associated with the infarction.

Pulmonary Vessels. The blood vessels of the lesser circulation are not dilated significantly by nitrites. Nitroglycerin, for example, does not relax isolated pulmonary arterial strips. The refractoriness of pulmonary vessels is not peculiar to the action of nitrites, because the pulmonary vascular responses to drugs, as a rule, are rather feeble.

Retinal Vessels. The nitrites dilate the retinal vessels, as can be verified by direct ophthalmoscopic observation of the fundus. Intraocular tension is increased and therefore caution should be observed in the employment of the drug in patients with potential glaucoma. Hirschfelder (1915) demonstrated that drugs acting on pial vessels also act in a like manner on retinal vessels. Similarly, the facial vessels respond to drugs in the same direction as do the cerebral. These three vascular beds, therefore, often respond as a unit, and the deep blush of the face has its intracranial and retinal counterparts.

Blood Pressure. The blood pressure usually falls after the administration of nitrites. The speed and extent of the decline depend on the dose and preparation of nitrite used, the route of administration, the original level of the blood pressure, and the presence of susceptibility or tolerance. The systolic pressure characteristically falls more than the diastolic, and this is true both for normal persons and hypertensive patients. The pulse pressure is therefore diminished. Although the absolute fall in hypertensive individuals is greater than in normal persons, the percentage fall is the same in health as in disease. The duration of the hypotensive effects of nitrites is longer in hypertensive patients than in normal subjects.

To illustrate some of these facts, certain clinical investigations may be cited. In a study of the effects of rather large doses of orally administered sodium nitrite (0.2 to 0.3 gram) to 10 normal persons and 29 patients with essential hypertension, Weiss and Ellis (1933) found that the action of the drug started within three to five minutes after ingestion. Although the blood pressure sometimes was unaffected in normal individuals it usually fell an average of 12 mm of mercury systolic and 10 diastolic, the fall persisting from one to two hours. In some instances, the fall in systolic pressure was three times as great, but the diastolic level rarely fell more than 15 mm of mercury. The vasodepressor action of nitrites lasted longer in the hypertensive cases, averaging two hours. The average decline in blood pressure was 35 mm systolic, 20 mm diastolic. Rarely, an extreme fall in pressure occurred, in one case being from 240/130 to 80/70. Symptoms noted in the two groups were unrelated either to the size of the dose or to the degree of the vasodepressor action, unless the fall in pressure was extreme. Headache, weakness, giddiness and faintness were the most common complaints. In a study of 50 patients with essential hypertension, Lueth and Hanks (1938), observed that a fresh solution of glyceryl trinitrate (0.4 mgm drug) caused an average fall in systolic pressure of 21 mm of mercury, or 10 per cent of the average systolic level of 220 mm for the group.

In Table 33 are listed the characteristics of the vasodepressor response of hypertensive patients receiving therapeutic doses of the common preparations of nitrites.

TABLE 33

BLOOD PRESSURE RESPONSE OF HYPERTENSIVE PERSONS TO THE NITRITES

NITRITE *	TIME OF ONSET OF FALL MIN.	TIME OF GREATEST FALL MIN.	EXTENT OF SYSTOLIC FALL MM HG	TIME OF RECOVERY MIN.
Amyl Nitrite	½ to 1	2 to 3	15 to 25	4 to 8
Nitroglycerin	1 to 2	5 to 10	15 to 30	25 to 40
Sodium Nitrite	5 to 20	25 to 40	25 to 40	60 to 150
Erythrityl Tetranitrate	15 to 30	30 to 50	30 to 40	180 to 300
Mannitol Hexanitrate	15 to 30	60 to 120	30 to 40	240 to 360

* Full therapeutic doses and usual routes of administration.

Action on the Heart. The nitrites exert no direct effect on the myocardium. Cardiac output is not altered in normal persons receiving large doses of sodium nitrite and decreases only insignificantly as a rule in hypertensive patients (Weiss and Ellis, 1933). In both normal and hypertensive individuals, the stroke volume output of the heart is diminished somewhat by nitrite medication, usually about 15 per cent, suggesting a decrease in venous return. The fact that no significant change in the minute volume output of the heart occurs after nitrites, even in the presence of a considerable drop in arterial blood pressure, rules out the possibility that the latter is due to any direct action of the drug on the ventricular muscle.

The *coronary vasodilatation* produced by nitrites may improve the blood supply to the myocardium when this is deficient due to pathological changes in the vessels. Myocardial anoxia, the functional basis of the pain of angina pectoris, may thereby be relieved and the heart enabled to work more efficiently. The pooling of blood in the postarteriolar vessels by the action of nitrites may diminish the venous return and temporarily lighten the burden on an insufficient myocardium, the basis for the use of nitroglycerin in patients with severe attacks of paroxysmal nocturnal dyspnea. Large doses of nitrites, poor spacing of medication or use of the drug in susceptible persons may cause marked falls in blood pressure which may impair the efficiency of the heart through the decrease in venous return and diminution in coronary blood flow, the latter being dependent within certain limits on the mean level of the systemic aortic pressure. In this manner, coronary blood flow may decrease despite the coexistence of coronary vasodilatation.

Cardiac Rate. The tachycardia noted after the inhalation of amyl nitrite is due to a carotid sinus reflex resulting in sympatho-adrenal discharge, which occasionally may be of sufficient magnitude temporarily to raise the blood pressure. The latter soon falls, however, despite the tachycardia. After administration of the other nitrites, changes in cardiac rate are less obvious, and chronic medication with nitrites usually causes no significant alteration in the heart rate. For example, Weiss and Ellis (1933) noted that the administration of 0.06 to 0.13 gram of sodium nitrite to normal or hypertensive persons caused inconstant changes in heart rate and that doses of 0.2 to 0.3 gram produced an average increase of only eight beats per minute. Rarely, a patient responds to nitrite medication with a marked tachycardia.

Pulse. After large doses of nitrites, the pulse is full and may be dicrotic in character. The full pulse occurs independently of any vasodepressor effect of the drug and is due to a relaxation of the large arteries of the extremities. Indeed, the greater fall in blood pressure in hypertensive as compared with normal individuals may be due in part to the relaxation of spastic larger arteries in the former group.

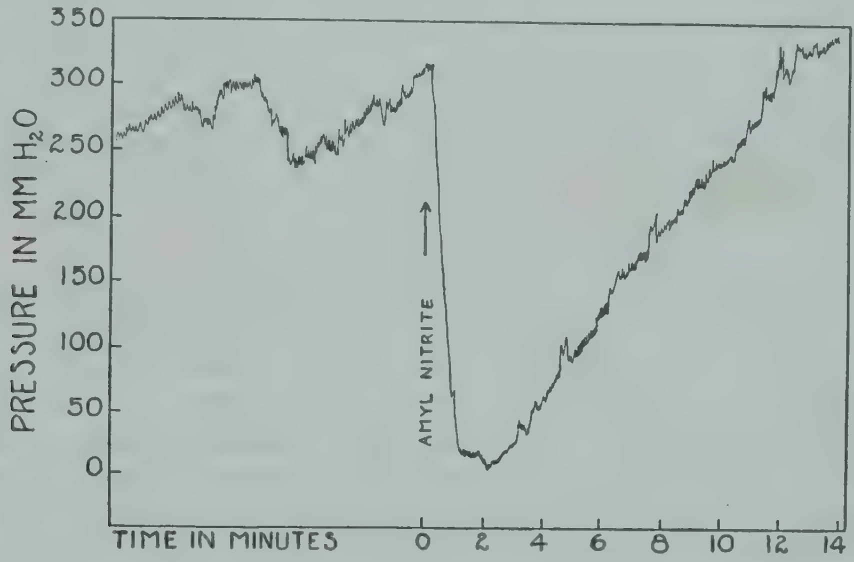

Figure 58. *The effect in man of the inhalation of amyl nitrite on the increased intrabiliary pressure produced by morphine.*

Kymographic tracing obtained by means of water manometer connected to a T-tube inserted into the common bile duct for prolonged biliary drainage. Note the rapid fall to zero in intrabiliary pressure and the subsequent rise to the previous level. (After Butsch, McGowan and Walters, 1936. Courtesy of *Surgery, Gynecology and Obstetrics.*)

Electrocardiogram. The electrocardiogram is not significantly altered by full therapeutic doses of nitrites. Even when nitrite-induced syncope occurs, the alteration in the complexes consists mainly of an increased amplitude of the T wave in the chest lead. This indicates that myocardial anoxia and depression do not occur even during extreme peripheral circulatory collapse due to the drug (Weiss and coworkers, 1937). Apparently, the coronary circulation remains adequate in patients without coronary disease.

Actions of Nitrites on Smooth Muscles. The relaxation of smooth muscle produced by nitrites is also evident in the bronchi, and in the gastro-intestinal and urinary tracts.

Bronchial Muscles. Nitrites relax the bronchial musculature. This can be shown experimentally in a number of ways, as for example by the relief of bronchial spasm induced in animals by peptone, histamine and pilocarpine. The inhalation of smoke from the burning of potassium nitrate is an old remedy for bronchial asthma and depends upon the presence of nitrites in the smoke.

Biliary Tract. The musculature of the gall bladder and biliary ducts is relaxed by nitrites. Evidence of this action in human beings has been presented especially by Butsch, McGowan and Walters (1936) who studied the responses of intrabiliary pressure to drugs in patients who had T-tubes inserted for prolonged biliary drainage following exploration of the common bile duct. The inhalation of amyl nitrite produced a dramatic and rapid fall of intrabiliary pressure elevated spontaneously or by morphine. Pain and other symptoms incident to the increased biliary pressure were promptly relieved (Figure 58). Glyceryl trinitrate (0.6 mgm) administered sublingually resulted in a more prolonged but less marked and less rapid decrease in intrabiliary pressure (Figure 59). Roentgenographic evidence showed that the nitrites relaxed the spasm existing at the duodenal entrance of the common bile duct.

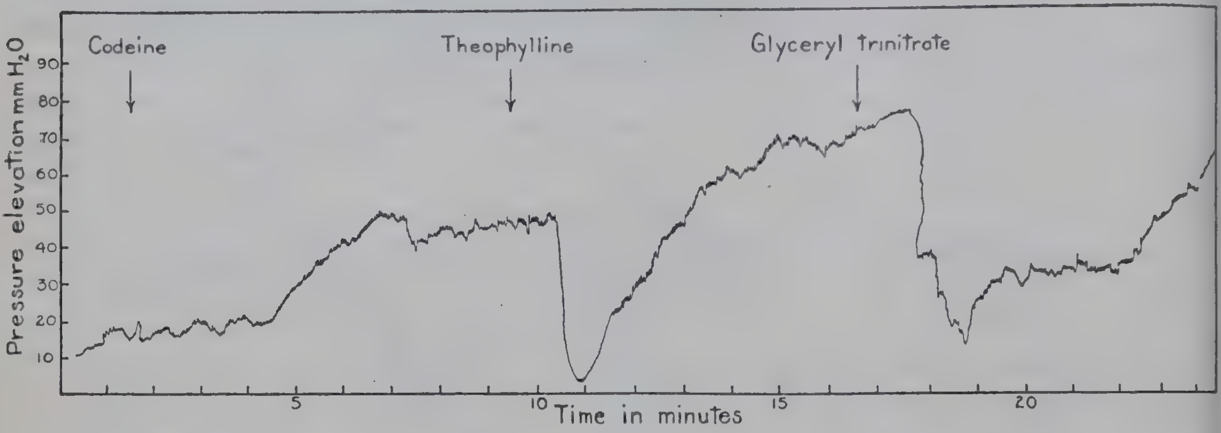

FIGURE 59. *The effect in man of theophylline and glyceryl trinitrate on the increased intrabiliary pressure produced by codeine.*

Kymographic tracing obtained by means of a water manometer connected to a T-tube inserted into the common bile duct for prolonged biliary drainage after exploratory operation. The subcutaneous injection of 60 mgm of codeine sulfate rapidly causes a marked increase in intrabiliary pressure which may persist for two hours or more. Theophylline ethylene diamine (0.24 gram intravenously) and glyceryl trinitrate (0.6 mgm sublingually) both produce a rapid but temporary fall to normal of intrabiliary pressure. Note that the effect of nitroglycerin is more sustained than that of theophylline. (After Butsch, McGowan and Walters, 1936. Courtesy of *Surgery, Gynecology and Obstetrics.*)

Gastro-intestinal Tract. Relaxation of the smooth muscle of the intestinal tract is also accomplished by nitrites, but the action is not evident unless spasm is present. The stomach is relaxed, intestinal peristalsis diminished, and pain due to spasm may be relieved (Beams, 1932; Beams and Barlow, 1932).

Genito-urinary Tract. The excised ureter is relaxed by nitrites and there is some evidence that a similar antispasmodic action on the intact ureter is manifested clinically. Nitrites also relax the uterus, but this action is not prominent or applicable therapeutically.

Metabolic Effects. The nitrites produce no significant alteration in *basal metabolic rate* in normal or hypertensive patients (Weiss and Ellis, 1933). After inhalation of amyl nitrite, the surface temperature of the flush area may rise markedly. Some heat loss occurs as the result of the increased peripheral circulation caused by nitrites. The *body temperature* ordinarily remains normal, however, due to adequate compensatory adjustments. In fevers, the nitrites may exert a mild antipyretic effect, but the wide use of sweet spirits of niter as a diaphoretic has become obsolete. The nitrites are definitely weak in their antipyretic action, and are no longer employed for this purpose. *Renal function* is either unchanged or depressed, in both normal persons, hypertensive patients and those with impaired kidney function. No correlation can be observed between changes in renal clearance and blood pressure following nitrites (Weiss and Ellis, 1933).

Nervous System. In therapeutic doses the nitrites usually exhibit no demonstrable effect on the central nervous system in man. The chemoreceptors of the carotid body, however, are sensitive to nitrites and by this mechanism the nitrites can produce changes in respiration. During the syncope produced by nitrites in susceptible patients or experimentally in normal persons assuming an immobile orthostatic posture, both the sympathetic and parasympathetic nervous systems are reflexly activated, the latter especially by cerebral anoxia (Weiss and associates, 1937).

Respiration. The respiratory rate and amplitude are both temporarily increased upon the inhalation of amyl nitrite. This is largely a respiratory reflex mediated through the carotid body, although the changes may result in part from the fall in blood pressure. Sodium nitrite, when injected into the carotid artery immediately below the region of the carotid sinus, causes intense bradycardia and hyperpnea, but does not do so if the chemoreceptor area is denervated (Heymans, Bouckaert and Dautrebande, 1931).

Vision. Transitory visual disturbances may occasionally be produced by the rapidly acting nitrites. Dark objects on a light background may appear to be surrounded by inner halos of yellow and outer ones of blue. These changes are probably related to the effect of nitrites on the retinal circulation.

Absorption, Fate and Excretion. *Amyl nitrite* is very volatile and readily absorbed from the lungs. It is thus administered only by inhalation. The drug is largely destroyed in the gastro-intestinal tract because the gastric juice acts on it to liberate nitrous acid which is then immediately decomposed. Amyl nitrite is therefore quite inactive when swallowed. Recovery has been reported after the ingestion of 12 cc (60 times the therapeutic dose). The drug also acts poorly by the hypodermic route.

Nitroglycerin is usually administered in the form of tablets placed under the tongue. Although not decomposed by the gastric juice, it is absorbed more efficiently by the sublingual than by the intestinal route. Nitroglycerin is also absorbed through the skin, a matter of importance in industry. The drug can be given hypodermically without pain, but is not employed in this manner.

Sodium nitrite is absorbed from the intestinal tract. Large doses may cause gastric irritation, nausea and vomiting due to the release of nitrous acid by the action of the gastric juice. After therapeutic doses, however, these symptoms are either absent or insufficient to interfere with oral administration of the drug. Sodium nitrite is therefore always given orally, usually in the form of tablets because solutions decompose in the bottle within a few days.

About 60 to 70 per cent of the absorbed nitrite disappears in the body. The exact fate of this fraction is unknown, but it may be converted in part to ammonia. The remainder is excreted in the urine in the form of nitrites and nitrates. The amyl radical of amyl nitrite is partly oxidized and partly excreted by the lungs.

Toxicology and Untoward Responses to the Nitrites. *Methemoglobin.* Excessive doses of any of the nitrites convert hemoglobin to methemoglobin. If methemoglobinemia is sufficiently marked, cyanosis and functional anemia result. The production of methemoglobin by nitrites can readily be demonstrated by the addition of sodium nitrite to shed blood, whereupon the characteristic chocolate color and spectrographic absorption bands can be detected. A similar change does not occur, however, when nitroglycerin is added to blood *in vitro.* Caution should be observed regarding the use of large doses of nitrites, especially in anemic patients. Severe poisoning and even death have been reported in a number of infants from nitrite-induced methemoglobinemia, the drug having been given as an antidiarrheal powder in the form of bismuth subnitrate. Certain bacteria of the normal intestinal flora, especially *E. coli,* reduce the nitrate ion to nitrite, and the latter may be absorbed in sufficient amount to cause fatality in infants ill with diarrhea. The presence of atypical flora, enteritis and liquid intestinal contents combine to accelerate the production and absorption of toxic amounts of nitrite. Bismuth subnitrate should therefore not be employed as an antidiarrheal powder, the subcarbonate being the preferred bismuth compound for this purpose. The peculiar therapeutic application of the nitrite-induced methemoglobinemia in the therapy of cyanide poisoning is fully discussed on page 701.

Intraocular Pressure. The mechanism of the rise of intraocular tension after nitrite administration has been mentioned. The possibility that a rise in pressure may occur, especially after the inhalation of amyl nitrite, enjoins caution in the employment of nitrites in patients with incipient glaucoma.

Headache. If headache develops after the use of nitrites it is usually transitory in character. The administration of the longer-acting nitrites, however, may result in severe headache in some patients. This is particularly true of erythrityl tetranitrate.

Intracranial Pressure. Due to the cerebral vasodilatation they produce, the nitrites may elevate the cerebrospinal fluid pressure. The rise in pressure may be so pronounced at times as to be a clinically undesirable side-action in some patients.

Nitrite Syncope. The nitrites are not entirely innocuous to the circulatory system when given in therapeutic doses. For example, there are numerous reports in the clinical literature indicating that marked untoward reactions may occur in susceptible patients. Cardiovascular collapse has been recorded after the administration of from 0.65 to 1.3 mgm of glyceryl trinitrate but occasionally it results from as little as 0.24 mgm (White, 1931; Proger and Ayman, 1932; Sprague and White, 1933). In a study especially designed to observe the cardiovascular reactions to nitroglycerin under basal conditions in 50 patients with essential hypertension and hypertensive heart disease, Lueth and Hanks (1938) recorded mild to severe reactions in nine individuals or 18 per cent, a higher incidence than is usually observed. The reaction is unpredictable and consists of nausea and vomiting, weakness, restlessness, pallor, cold sweat, syncope, collapse and involuntary passages of urine and feces. The patient usually recovers within an hour and procedures which facilitate venous return, such as the head-low posture, deep respirations and movements of the extremities, are effective in preventing the syncope or hastening recovery. Epinephrine is not reliable and indeed is often contraindicated.

Mechanism of the Nitrite-Induced Syncope. Weiss, Wilkins and Haynes (1937) have investigated in detail the mechanism of nitrite-induced syncope in seven healthy young adults. Under basal conditions, the cardiovascular responses and symptomatology resulting from the oral ingestion of 120 to 180 mgm of sodium nitrite were recorded both for the horizontal and static vertical positions. Few if any symptoms or vascular changes result as long as the subject remains horizontal. In Figure 60 and its accompanying legend is described the typical vascular collapse precipitated by the assumption of the immobile upright position. The condition is promptly relieved when the individual is returned to a horizontal posture. The marked decrease in pulse rate occurring immediately before the syncope is not the cause of the latter. It is prevented by two mgm of atropine and is due to the stimulation of the vagal nuclei by cerebral anoxia. The speed of onset of syncope after the patient is placed in the vertical position varies with the individual, the dose of nitrite and the degree of the upright posture.

Nitrite syncope exemplifies peripheral circulatory failure in its pure form and resembles that seen in pneumonia and other infectious diseases, anaphylactic shock, etc. Nitrite collapse is due to a pooling of blood in the postarteriolar vascular beds and not to a primary fall in blood pressure due to arteriolar dilatation. Indeed, the arterioles are reflexly constricted in an attempt to maintain the circulation, as indicated by a decrease in blood flow in the hand kept at 32 C. but not in the warmed hand (45 C.). The lack of arteriolar dilatation is also established by the well-maintained diastolic pressure. The small pulse pressure

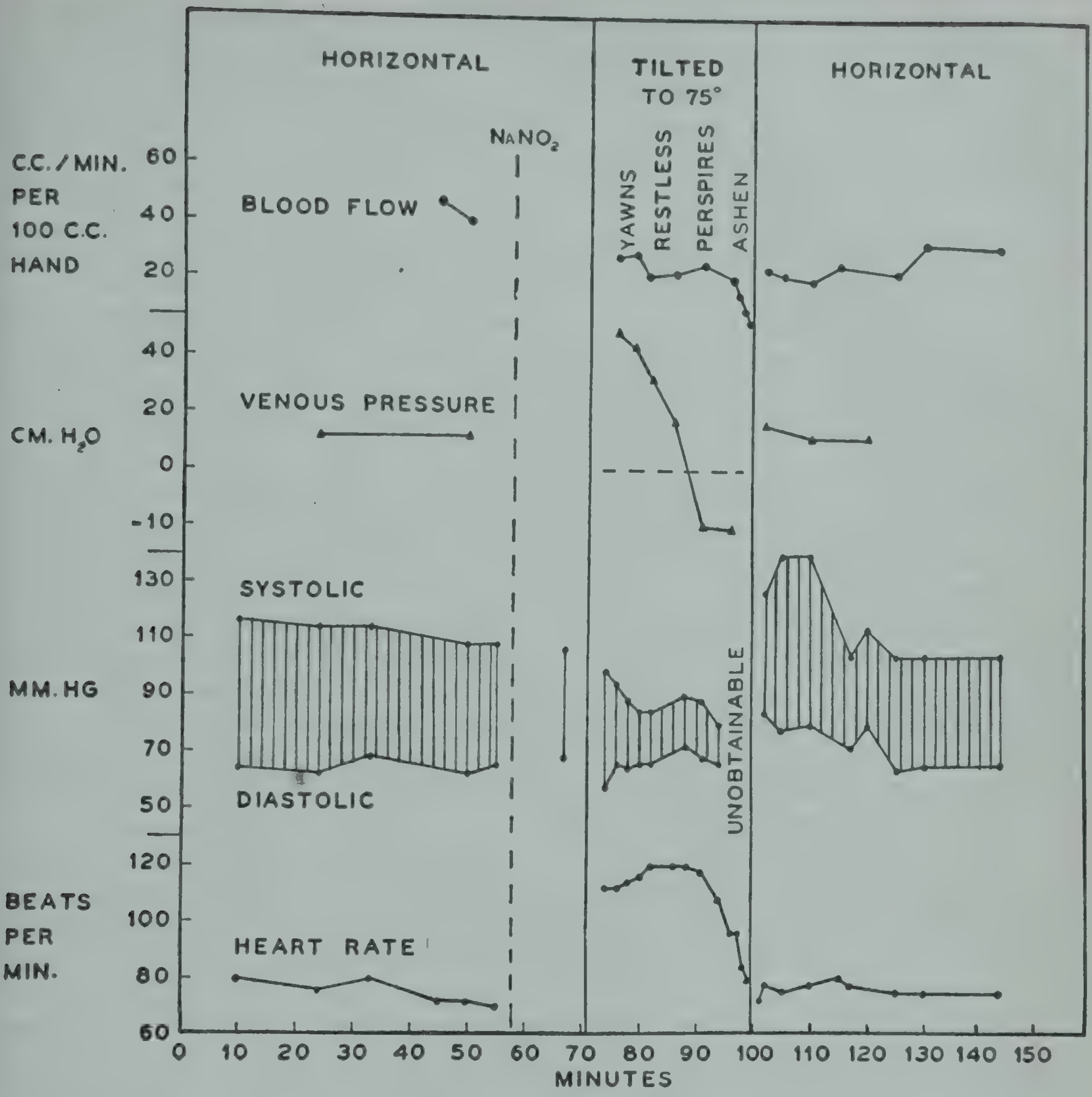

FIGURE 60. *Circulatory collapse induced by sodium nitrite.*

Normal robust male, aged 28, given 0.18 gram of sodium nitrite by mouth. While remaining in the horizontal position, no essential change occurred in the blood pressure, blood flow (through the warmed hand), or heart rate and there were no subjective symptoms. When the subject was tilted to the upright position (75°), marked changes occurred in rapid succession. Yawning appeared and became progressively more prominent; the respirations deepened and assumed a sighing character; restlessness, belching, and borborygmus were noted and a cold perspiration broke out over the entire body surface. In about 20 minutes, the skin was ashen gray, the subject became drowsy, the pupils were dilated and the picture resembled clinical vasomotor collapse. Note the following cardiovascular changes accompanying the assumption of the upright position: The blood flow was well maintained until shortly before collapse, when it rapidly fell to zero. The arterial pulse pressure became quite narrow soon after the tilting, due mainly to a fall in systolic pressure, the diastolic level even rising somewhat. The radial pulse became small and thready, and finally imperceptible except for short periods after each deep respiration. The venous pressure fell rapidly until a level was reached which was below the hydrostatic level of the right auricle. The heart rate rose to 120 beats per minute until shortly before syncope when it slowed markedly, at which time the blood pressure was unobtainable. Vision became dim, muscular power was lost and unconsciousness ensued. The patient was immediately returned to the horizontal position and regained consciousness within 20 seconds. All circulatory abnormalities promptly returned to normal. Nitrite syncope is due to a pooling of the blood in the postarteriolar vascular bed. (After Weiss, Wilkins and Haynes, 1937. Courtesy of the *Journal of Clinical Investigation*.)

and low systolic pressure are due to the decreased venous return to the heart. Thus nitrite shock is due to a decrease in the "effective blood volume," that is, a disproportion between the circulatory blood volume and the volume capacity of the peripheral vascular bed. Due to the peripheral pooling of blood in the venous system after large doses of nitrites, the circulatory system is unable to adjust itself to the strain of the orthostatic position (Wilkins, Haynes and Weiss, 1937).

The reflex constriction of the arterioles which may occur in nitrite syncope aggravates the circulatory status by decreasing blood flow and increasing tissue anoxia. For this reason, peripheral vascular collapse characterized by decreased venous tone, postarteriolar congestion and increased peripheral arteriolar resistance is not prevented by and does not respond to epinephrine, and may even be made worse by agents causing arteriolar spasm (Wilkins, Weiss and Haynes, 1938).

Treatment of Untoward Reactions to Nitrites. Death from nitrite poisoning is rare. Symptoms are referable mainly to cardiovascular collapse as described and to methemoglobinemia, and treatment is directed against these two features. Inhalation of oxygen, injection of small doses of methylene blue (page 1032) or transfusion of blood may be resorted to if methemoglobinemia is marked. Blood transfusion also aids the state of shock. Epinephrine and other vasopressor agents should not be used for the reasons already stated. The head-low position and movements of the extremities aid in the return of venous blood to the heart and are measures not to be scorned. If shock is severe, other symptomatic measures employed in shock therapy should be utilized. Preliminary gastric lavage should be instituted if the drug was taken orally.

Tolerance. Tolerance develops to the nitrites with the continued use of any member of the group. Tolerance begins to appear within a few days and is fairly well established in about two to three weeks. As tolerance becomes more and more pronounced, larger doses of the nitrites must be used to obtain the original cardiovascular effects, and finally such large doses are necessary that medication is unsafe because of the danger of methemoglobinemia. Furthermore, if sodium nitrite is used, undesirable gastric symptoms become prominent. The degree to which tolerance may develop is seen in the fact that cases are on record in which 0.3 to 0.4 gram of nitroglycerin taken orally caused no ill effects (Stewart, 1905). Cessation of administration of nitrites for several days to two weeks invariably reestablishes the original degree of susceptibility to the cardiovascular actions of the drug. The mechanism of tolerance to the nitrites is unknown.

Cross-tolerance also occurs and extends to all members of the nitrite group. The belief that sodium nitrite and erythrityl tetranitrate do not manifest the phenomenon of cross-tolerance is probably incorrect, although it is somewhat more difficult to develop tolerance to sodium nitrite and erythrityl tetranitrate (Myers and Austin, 1929; Crandall and coworkers, 1931).

Fortunately, tolerance to the headache induced by nitrite occurs more readily than to the hypotensive action of the drug (Crandall and coworkers, 1931). It is interesting to note that workers in munitions factories may suffer from headaches caused by nitroglycerin for the first few days of their employment; but after a short interval, due to the development of tolerance, they no longer notice ill effects. After a vacation of a week or two, however, they again suffer headaches upon resumption of work, susceptibility having been reestablished by cessation of exposure. For this reason, many workers learn to maintain their tolerance while on vacation by rubbing nitroglycerin on their skin.

In the clinical use of nitrites, the avoidance of tolerance can be facilitated by employing the smallest effective dose to initiate therapy, so that the dosage may be increased as tolerance develops. Also, the nitrites should not be prescribed continuously for more than two or three weeks, but rather they should be alternated with other drugs. In hypertension, the sedatives may be employed while the nitrites are discontinued; in angina pectoris, perhaps the xanthines may be similarly used. Many disappointments in chronic therapy with nitrites arise from ignoring the two foregoing simple rules.

Contraindications. Contraindications to the use of nitrites are few, and are relative rather than absolute. They have been mentioned but may be summarized at this point. In patients with marked anemia, increased intraocular pressure or increased intracranial pressure, the nitrites should be prescribed with caution. If the nitrites are used for diagnostic purposes in patients with acute coronary thrombosis, care must be exercised in regard to dosage. The nitrites should not be employed in persons who manifest idiosyncrasy to them, especially of a syncopal nature.

Preparations, Dosage and Routes of Administration. *Amyl Nitrite,* U.S.P., B.P. This is a clear, yellow, volatile and inflammable liquid with a fruity odor and a pungent aromatic taste. It is marketed in fragile glass ampules called "pearls," each of which contains a therapeutic dose of 0.2 cc. The pearl is crushed in a handkerchief and the contents inhaled. Amyl nitrite pearls are the most costly of the preparations of nitrite.

Tablets of Glyceryl Trinitrate, U.S.P., B.P. (Tablets of Nitroglycerin; Trinitrin Tablets). Nitroglycerin is a very explosive yellowish fluid. It is incorporated in tablets which usually contain 0.6 mgm of the drug (B.P., 0.5 mgm). The dose is one or two tablets placed under the tongue. Nitroglycerin tablets become inert in time or if exposed to the air. This is a frequent cause of disappointment in the use of the drug.

Spirit of Glyceryl Trinitrate, U.S.P. (Spirit of Nitroglycerin; Solution of Glyceryl Trinitrate, B.P.). This is an alcoholic solution containing one per cent of nitroglycerin. The dose is 0.06 cc (one minim) dropped under the tongue, the equivalent of 0.6 mgm of nitroglycerin. The spirit of nitroglycerin is more cumbersome to employ than tablets of the drug but has the advantage of retaining its potency. Great caution must be observed to prevent dangerous explosions which may occur if any of the solution is spilled and the alcohol wholly or partially lost by evaporation. Should spilling occur by accident, a solution of sodium or potassium hydroxide must be poured over it immediately to decompose the nitroglycerin.

Sodium Nitrite, U.S.P., B.P. Sodium nitrite is a white to slightly yellow crystalline powder. Although the salt is freely soluble in water, it is unstable in solution and is therefore dispensed in the form of tablets or capsules. The dose is 30 to 60 mgm given orally.

Diluted Erythrityl Tetranitrate (Diluted Erythrol Tetranitrate), U.S.P., B.P. This preparation consists of a mixture of erythrityl tetranitrate and lactose in equal parts. It is usually dispensed in tablet form for oral use. The dose of the diluted drug is 30 to 60 mgm. Erythrityl tetranitrate is also available in undiluted form in 15 and 30 mgm tablets (Erythrol Tetranitrate, Undiluted, N.N.R.).

Mannitol Hexanitrate. This drug is the nitrate of mannitol, a hexahydroxy-alcohol. It is fairly expensive, somewhat difficult to obtain in the United States, and is marketed in tablet form for oral use. The dose is 15 to 60 mgm.

Spirit of Ethyl Nitrite (Spirit of Nitrous Ether, Sweet Spirit of Nitre), U.S.P., B.P. This preparation consists of approximately four per cent of ethyl nitrite (B.P., approximately two per cent) in 90 per cent alcohol. It is unstable and unreliable, and is little used in therapeutics. The dose is two cc, taken orally.

Therapeutic Uses. *Angina Pectoris.* The nitrites are commonly employed in patients with angina pectoris, both for the immediate relief of the acute attacks of pain, and also for the prevention of seizures.

Relief of the Immediate Attack. The nitrites act in the relief of anginal pain by producing coronary vasodilatation. While it cannot be contended that arteriosclerotic coronary arteries readily respond to the nitrites by dilatation, yet it is quite likely that collateral vessels expand sufficiently to allow more blood to reach the anoxic areas of the myocardium. It should be stated, however, that there are investigators who are inclined to question the efficacy of nitrites for the relief of acute attacks. Gold and associates (1937), for example, studied the ability of ambulatory clinic patients to distinguish between the effects of glyceryl trinitrate and placebos. Of 60 patients, 49 (82 per cent) reported relief of pain during acute attacks by the use of the drug. Of 18 cases in which a soluble placebo was substituted, 14 (78 per cent) reported similar relief of symptoms. It is recognized, of course, that a characteristic of angina pectoris is the brevity of the attack of pain, and the immediate interruption of physical activity necessitated by the attack also contributes to the rapid relief which occurs spontaneously. For this reason it is extremely difficult for the patient or physician to judge the efficiency of drug therapy, and one is never certain in a particular instance whether relief obtained following medication was entirely specific or due in large measure to the spontaneous cessation of pain. Nevertheless, the nitrites are among the most potent coronary vasodilators clinically available, and continue to be employed for the acute pain of angina pectoris. In a careful quantitative clinical investigation in 11 patients with angina of effort, Wayne and Laplace (1933), utilizing an exercise tolerance test, found in 10 of the 11 cases that the inhalation of amyl nitrite caused measurable (but not considerable) reduction in the duration of pain.

Only the rapidly acting nitrites can possibly offer relief during the acute anginal episode. These are *amyl nitrite* and *nitroglycerin. Amyl nitrite* by inhalation acts within 30 seconds and the patient is instructed to crush a pearl of the drug in a handkerchief and inhale the vapor at the first indication of an attack. Objections to amyl nitrite are its odor, the marked flushing, throbbing in the head, and occasional nausea and vomiting which it causes, as well as its expense. Some patients prefer to allow the attacks to pass off spontaneously rather than experience the side-effects produced by amyl nitrite. In the long-lasting attacks of pain which occur spontaneously rather than being induced by exercise (such as described by Lewis, 1931), amyl nitrite may give dramatic relief, and it is on the basis of such results that the reputation of the drug probably rests.

Nitroglycerin tablets are also frequently employed for acute anginal episodes. Two or three minutes are required before the action of the drug is manifest, however, and the patient must therefore be instructed to place the tablet under his tongue at the first premonition of an impending seizure. If one 0.6 mgm tablet is insufficient, two or more may be taken sublingually at once. Some believe that nitroglycerin is used too timidly and have no hesitation in giving eight to 10 tablets over a two to three hour period, if necessary, for recurrent attacks of pain. The wisdom of this procedure may be questioned in view of cases of vascular collapse which have resulted from the injudicious use of nitroglycerin. Patients should be forewarned of the possibility of dizziness, flushing, and cranial throbbing, assured that these are harmless although unpleasant side-actions, and told to assume a horizontal position should symptoms be marked.

Nitroglycerin may also be employed as a diagnostic agent to differentiate between an acute attack of angina pectoris and the pain of coronary thrombosis. The pain of acute coronary thrombosis is uninfluenced by nitrite medication. Considerable caution is necessary because the patient with a fresh myocardial infarction is in a state of collapse. A single dose of 0.6 mgm may be placed under the tongue if the blood pressure is not too low, and the effect carefully noted. If pain persists, the existence of coronary occlusion is more likely. A second tablet of nitroglycerin may be given only after a suitable interval.

Prophylactic Use. The nitrites have a firmer therapeutic footing in the prophylactic management of patients with angina pectoris. The longer-acting nitrites are to be preferred for the purpose of relieving the severity and decreasing the frequency of attacks of pain. *Erythrityl tetranitrate* may be given orally in a dose of 30 to 60 mgm three times daily. *Sodium nitrite* may be employed in a dose of 15 to 60 mgm every three or four hours, and is the cheapest salt of the group. *Mannitol hexanitrate* in a dose of 15 to 60 mgm three times daily may also be prescribed. Some clinicians prefer small doses of *nitroglycerin,* employing 0.1 mgm of the drug hourly. Indeed, Riseman and Brown (1937), in a careful study of the efficacy of many cardiovascular drugs in 26 patients with angina pectoris, found nitroglycerin (0.1 mgm hourly) to be the most effective of all and to render about 33 per cent of the cases free from attacks. Nitroglycerin also allowed a greater increase in the ability to perform the exercise tolerance test than other agents employed for angina pectoris.

One must start with the smallest effective dose of nitrites and increase this as tolerance develops. After several weeks, a rest period from nitrite medication should be allowed during which xanthines or sedatives may be used if necessary. When the nitrites are resumed, the lower dose level is again employed.

In the discussion of the value of xanthines for chronic medication in patients with angina pectoris, it is pointed out that clinical studies, of a questionnaire character, appear to discredit their value as coronary vasodilators, whereas animal experimentation and exercise tolerance tests indicate definite improvement in the coronary circulation (page 282). The poor results obtained in this manner with xanthines have been confirmed by Master and associates (1939) and extended to include nitroglycerin, sodium nitrite and a large number of other drugs. They report that in a study of 116 ambulatory patients attending an angina pectoris clinic better results were obtained with a placebo (lactose) than with the xanthines, nitrites, sedatives, etc.

Nevertheless, in regard to nitroglycerin, Wayne and Laplace (1933) have carefully studied 11 selected cases of angina of effort for their exercise tolerance before and after 0.65 to 2.0 mgm of the drug. In eight patients, an increased amount of effort was required after nitroglycerin before pain appeared and in two it was impossible to elicit pain from exercise after medication, the patients stopping due to dyspnea or fatigue rather than pain. The increase in work allowed by nitroglycerin in the group varied from 30 to 150 per cent, and the duration of the exercise-induced pain was somewhat shortened. These facts are clearly shown in Figure 61, which also indicates the changes in blood pressure and cardiac rate which occur. It is evident that the beneficial effects of nitroglycerin are unrelated to any vasodepressor action, the relief of pain being unassociated with the time or extent of the fall in systolic pressure. Often pain occurred at a time when the blood pressure was no higher than it was at rest. This is consistent with all present concepts concerning the etiology of the pain of angina pectoris and differs sharply from the view held by Brunton which formed the original basis for the use of nitrites in the anginal syndrome. The efficacy of nitroglycerin was found to last about one-half hour, on the basis of the exercise test employed. Erythrityl tetranitrate, in a limited study by Wayne and Laplace (nine cases), was found to be less effective than nitroglycerin, as was also theophylline ethylene diamine (four patients).

Other forms of therapy in angina pectoris include the use of alcohol, xanthines and sedatives, and in selected cases surgical measures such as upper thoracic sympathetic ganglionectomy, paravertebral injection of alcohol into the upper thoracic sympathetic ganglia, total thyroidectomy, and omental or pectoral muscle transplants to the epicardium.

Hypertension. Nitrites are employed in the symptomatic treatment of hypertension of the "essential" type. Although it is possible to lower the blood pressure of hypertensive patients by the use of various drugs, the therapeutic problem involved is much more basic than this. Such therapy is purely symptomatic and the underlying pathology is unaltered. The results of attempts to lower the blood pressure are most unsatisfactory as a rule. Although it is not difficult for the physician to accomplish a fair degree of manometric success, this is not always rewarded by a parallel relief of the patient's symptoms. Indeed, the patient may feel worse when his blood pressure is lowered.

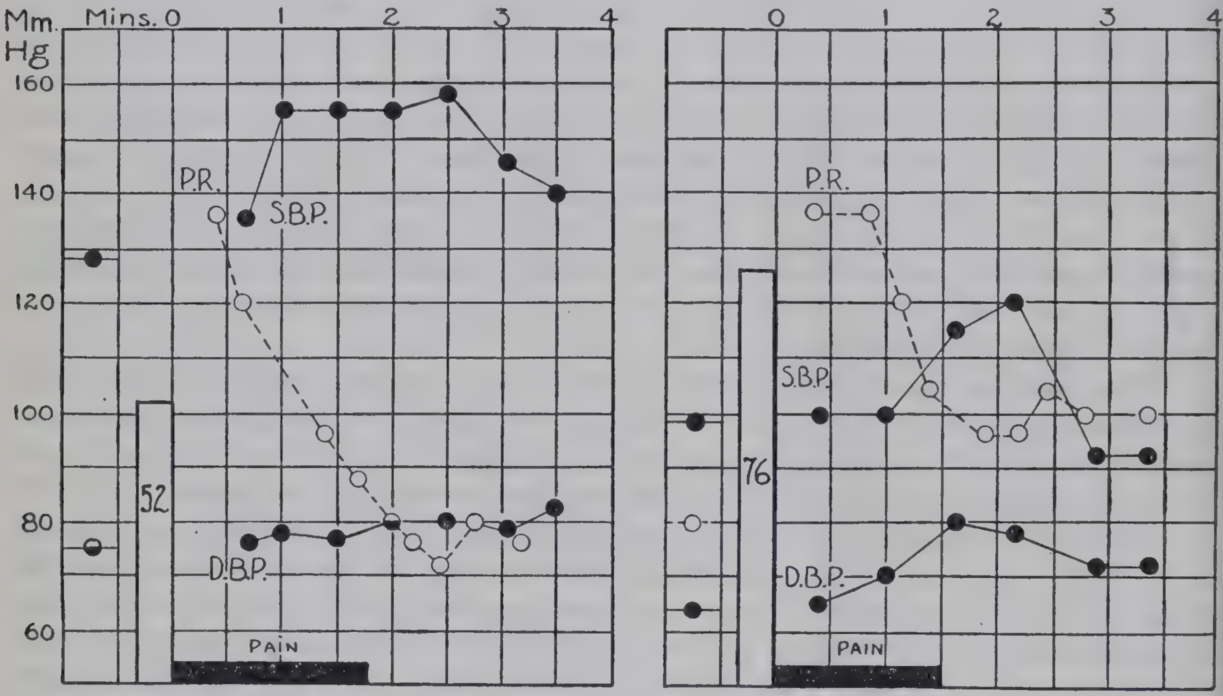

FIGURE 61. *The effect of nitroglycerin on the exercise tolerance, duration of pain, blood pressure and pulse rate in a case of angina pectoris.*

Male subject, aged 61, arteriosclerotic heart disease, angina of effort. Marked atheromatous obstruction of the main branch of the left coronary artery was found at autopsy. Chart on left shows control test; that on right the test repeated several minutes after the administration of 1.3 mgm of nitroglycerin. Figures in unshaded vertical columns represent the number of efforts (staircase exercise tolerance test) performed before pain was experienced. Solid horizontal columns represent duration of pain. Nitroglycerin increased the exercise tolerance approximately 50 percent and diminished slightly the duration of pain. Note that the blood pressure at the time of onset of pain is not significantly higher than the normal resting level (see text). (After Wayne and Laplace, 1933. Courtesy of *Clinical Science*.)

Sooner or later in the course of his disease, nearly every hypertensive patient is placed on a trial period of therapy with vasodepressor drugs, and the nitrites are most commonly used. Treatment is perhaps especially indicated if the patient is seen very early and has a rather labile blood pressure, if a cerebral vascular accident or hypertensive encephalopathic episode is imminent, or if marked symptomatic relief is experienced. The nitrites to be selected are naturally the long-acting ones, that is, the preparations given above for the prophylactic treatment of angina pectoris. They are employed in the same doses, at the same intervals and with the same precautions. Especially should tolerance be avoided by interpolating periods of rest from nitrites, during which sedatives may often be used to good advantage.

Bismuth subnitrate has also been employed for the symptomatic therapy of essential hypertension, being introduced for this purpose by Stieglitz (1930). The dose is one gram given orally three times daily. The drug is gradually converted to nitrite in the intestine and it is thought that the slow continuous absorption of nitrite produced in this manner may have certain advantages in hypertensive patients. Clinical results on the whole have been rather disappointing with bismuth subnitrate. It appears that the drug provides a rather uncertain and fortuitous way of obtaining the entrance of nitrite ions into the body. If nitrites are indicated, better preparations are available.

The status and disadvantages of nitrite therapy of essential hypertension have been well summarized by Weiss and Ellis (1933), whose conclusion regarding sodium nitrite holds also for other nitrites and vasodilator therapy in general. "Any vasodilating drug which fulfills the criteria demanded in the treatment of arterial hypertension should have a constant, sustained action, should act by dilating the arterioles over all the constricted areas, should not give rise to unpleasant symptoms or side-effects and should maintain the normal functions of the organs, particularly of the heart and kidneys. These criteria are not fulfilled by the inconstant and transitory action of sodium nitrite. The drug at times produces severe unpleasant symptoms, which are frequently unrelated to the magnitude of the decrease in blood pressure, and may cause depression of renal activity. Although sodium nitrite may have some place in the treatment of vascular crises associated with hypertension, it is of no value in the daily treatment of the condition, and its employment in patients in whom renal insufficiency already exists is irrational. . . . The use of sodium nitrite in the routine treatment of arterial hypertension with the hope of maintaining the blood pressure at a relatively low level is illogical and dangerous."

Asthma. For acute attacks of bronchial asthma, the nitrites are considerably less effective than epinephrine or theophylline, but nevertheless they are occasionally used. Potassium nitrate may be incorporated with stramonium in a powder to be burned on a plate, and the smoke is then inhaled. The nitrate not only insures combustion but the smoke also contains nitrites in addition to the stramonium alkaloids.

Gastro-intestinal Uses. The nitrites are not very serviceable for the relaxation of gastro-intestinal spasm. Amyl nitrite or nitroglycerin, however, may be employed in *lead colic,* where they may act not only to relax the intestinal musculature but also the splanchnic blood vessels. In an occasional case of *pylorospasm,* the nitrites may give satisfactory relief. During *fluoroscopic examination* of the stomach and duodenum, the administration of amyl nitrite or nitroglycerin may assist in the differentiation between organic defects and deformities due to functional spasm (Beams, 1932). Benzedrine and atropine may be similarly employed. The rapidly acting nitrites may be effective in the relief of pain in acute *biliary colic,* as indicated in Figures 58 and 59. Several investigators have reported successful results in biliary dyskinesia and colic from the sublingual administration of nitroglycerin (McGowan, Butsch and Walters, 1936; Walters and associates, 1937; Best and Hicken, 1938; McGowan and Henderson, 1940). Recurrent attacks of biliary pain following cholecystectomy may be adequately relieved in some patients by the judicious use of the drug. Occasionally, residual small stones in the common duct or inspissated bile may be released as a result of the antispasmodic action of the nitrites.

Acute Pulmonary Edema. Although morphine, theophylline, digitalis and other measures are paramount in the treatment of acute pulmonary edema secondary to left ventricular failure, nitroglycerin may be rationally but cautiously employed in an attempt temporarily to store blood in the peripheral capillary and venous depots and thus reduce the venous return to the heart. This therapy is functionally similar to venesection.

Miscellaneous Uses. The nitrites are occasionally effective in certain cases of *migraine*. The mechanism of relief is not clear but is probably related to changes in the meningeal vessels. The nitrites have also been employed in *toxic amblyopia* (*e.g.,* tobacco amblyopia) to improve retinal circulation. If the aura is sufficiently long, the inhalation of amyl nitrite may abort an *epileptic seizure.* In *uretral spasm* or *colic,* the short-acting nitrites may sometimes afford relief. In severe generalized *pruritus,* such as occurs in dermatoses, jaundice, Hodgkin's disease, leukemia cutis, etc., moderate or complete relief may follow the use of glyceryl trinitrate or erythrityl tetranitrate when other measures have failed. The mechanism of the antipruritic action is probably related to vascular changes in the skin. Symptoms due to circulatory effects of the drugs are common and may limit therapy (Prinzmetal, 1934). The use of nitrites in *cyanide poisoning* is discussed on page 701.

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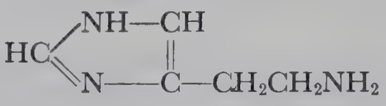
CHAPTER 31

HISTAMINE, THIOCYANATES AND MISCELLANEOUS CARDIOVASCULAR DRUGS

HISTAMINE

Histamine is a drug of considerable academic interest but little therapeutic importance. It is a powerful vasodilator, although its many side-actions often preclude the possibility of its clinical application for this purpose.

Chemistry. Histamine is β-iminazolylethylamine, a decarboxylation product of the amino acid histidine. It provides an excellent example of the fact that decarboxylation of an amino acid often results in a compound of marked pharmacodynamic activity. The chemical structure of histamine is as follows:



Histamine

Distribution. Histamine is widely distributed in tissues of plants and animals. It was identified first in ergot by Barger and Dale in 1910 although the compound had probably been isolated from soy bean but not identified by Yoshimura a year previously. The manner in which histamine is combined and stored in the animal body is an unsolved problem. An amount, which would be toxic if it were liberated, is present in a bound and inactive form in the tissues of all mammals. Histamine has been detected in every tissue, but by far the highest concentration is present in the lung. Its physiological significance at this locus cannot be stated. Leukocytes also contain appreciable amounts of histamine. Histamine can be formed by certain bacteria from the amino acid histidine and there is evidence that such a reaction can occur in the gastro-intestinal tract of man. It is possible to obtain from human feces both histamine and an organism capable of converting histidine to histamine. These facts do not provide a sound basis for the claim that histamine causes the so-called "autointoxication" syndrome.

Pharmacological Actions

Perhaps no other drug has the wide variety of actions possessed by histamine. There is hardly a tissue which will not respond in some way to this remarkable agent. The versatility of action coupled with the ubiquitous distribution of histamine in the animal organism has provided the basis for innumerable theories of the physiological function of the chemical. The possible relationships between the pharmacological actions and the physiological rôle of histamine will be pointed out as occasion offers.

Cardiovascular System. *Capillaries.* Histamine is a powerful dilator of capillaries. The action is a direct one on the contractile mechanism, and the response of the capillaries is independent of innervation and is not blocked by atropine. With large doses, the capillaries may dilate to such a degree that their permeability is altered. As a result there is a loss of plasma protein and fluid through the capillary wall into the extracellular spaces. When histamine gains access to the systemic circulation, all the capillaries of the body participate in the reaction. Dilatation of the capillaries of the skin is quite evident and is most marked over the blushing area. The skin temperature rises. After intradermal injection of histamine, an interesting local reaction occurs at the site of administration. This consists of dilatation of the capillaries in direct contact with the drug, a diffuse flare due to dilatation of surrounding arterioles resulting from local axon reflexes and, within a few minutes after the injection, an area of edema corresponding to the previous distribution of the capillary dilatation. The remarkable similarity noted by Lewis (*see* Lewis, 1934) between this reaction and the "triple response" to various types of stimulation of the skin has led to the conclusion that a histamine-like body (H-substance) or histamine itself may be liberated in response to tissue injury.

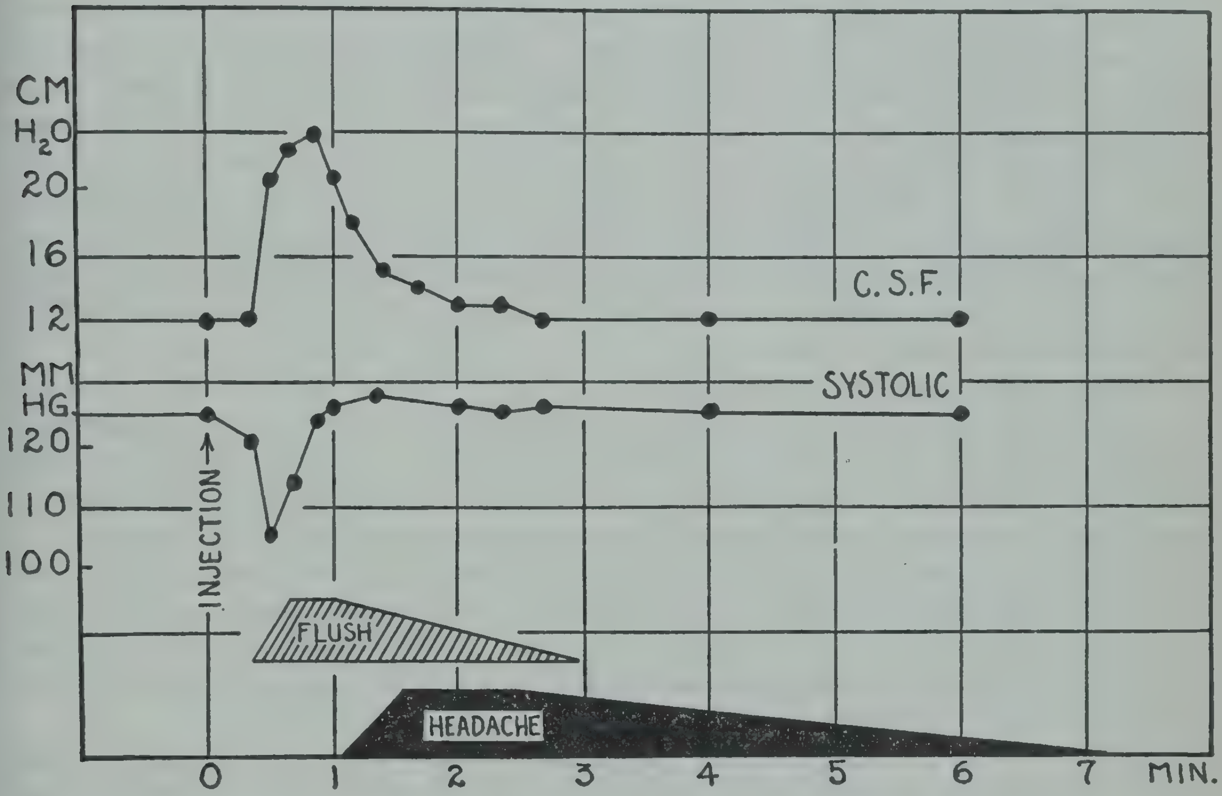


Figure 62. *Histamine headache.*

Chart showing the events which follow the intravenous injection of 0.1 mgm of histamine phosphate in a normal subject. Within 20 seconds after the injection, the face flushes, the pulse quickens, the blood pressure falls and the cerebrospinal fluid pressure rises. The curve of the cerebrospinal fluid pressure runs nearly parallel to the intensity of the facial flush. Observe that the headache does not commence until the blood and cerebrospinal fluid pressures have returned toward normal. Headache does not appear during the continuous infusion of histamine. Histamine headache, once initiated, can be interrupted by a second injection of histamine, or by any other procedure which raises the cerebrospinal fluid pressure or quickly lowers the arterial blood pressure. It is suggested that the headache is due to a stretching of sensitive structures lying close to the meningeal arteries. (After Pickering, 1933. Courtesy of *Clinical Science.*)

Arterioles. The action of histamine on arterioles changes as one ascends the zoological tree (Dale, 1929). For example, in rodents the drug produces marked arteriolar constriction; in cats, a slight arteriolar constriction; in the dog, monkey and man, arteriolar dilatation.

Special Vascular Beds. In addition to the general effects on blood vessels, histamine has specific actions on the circulation of different organs, varying with the species. For example, in one species there may be marked constriction of the coronary arteries; in another, dilatation. In the dog, histamine constricts the hepatic vein. Such reactions for the most part are only of academic interest. However, the action of the drug on the cerebral circulation is worthy of mention. Following the administration of histamine the vessels of the meninges and brain are dilated. Accompanying these circulatory changes there is an increase in cerebrospinal fluid pressure. The characteristic headache which follows the administration of histamine has been correlated with the changes in cerebral circulation (Pickering, 1933) (Figure 62) and the pain probably arises from the dura (Pickering, 1939). The fact that histamine causes headache has led some to believe that many of the symptoms of chronic constipation may arise from the intestinal absorption of histamine. There is no valid evidence for this assumption. The visual disturbances which follow the administration of histamine have been attributed to the vasodilatation of the retinal vessels and to the resulting sudden increase in intraocular tension.

Heart. Histamine has no pronounced direct cardiac action. The isolated perfused heart responds to low concentrations with an increase in rate and amplitude of contraction. If the concentration is increased, the muscle is weakened and disturbances in conduction may appear. In human subjects, it has been observed that when histamine is continuously infused intravenously at the rate of 0.02 to 0.04 mgm per minute the heart rate and cardiac output are increased (Weiss, Robb and Ellis, 1932). This is not the result of a direct cardiac stimulation but rather a compensatory reflex response to the vasodilatation. Observations on experimental animals indicate that histamine increases the rate of coronary blood flow (Essex and coworkers, 1940).

Blood Pressure. The extreme dilatation of arterioles and capillaries by histamine results in a marked fall in blood pressure. After small doses of histamine, the recovery from this fall is rapid. The two factors responsible for the recovery are the rapid destruction of histamine in the body and the elicitation of effective compensatory cardiovascular reflexes acting through sympathetic cardioacceleration, vasoconstriction and discharge of epinephrine. In fact, epinephrine itself in suitable doses can completely antagonize the vasodepressor action of histamine and many of its other actions as well. Weiss and collaborators, in the experiments cited above, noted that when histamine was infused intravenously reflex compensatory reactions were sufficient to prevent marked fluctuations in blood pressure, the systolic pressure remaining unaltered.

Histamine Shock. After large doses of histamine are administered, the fall in blood pressure may be pronounced and persistent, and histamine shock ensues. Histamine shock experimentally produced in animals has been analyzed in detail by Dale and Laidlaw (1919). The primary cause of the shock is excessive dilatation of the capillaries. This allows an escape of plasma from the circulation and a discrepancy results between the volume capacity of the circulatory system and the circulating blood volume. Such a discrepancy is the basic pathological physiology of shock of many varieties. The heart continues to beat rapidly and forcibly, but cardiac output is diminished as a result of stasis of blood in the capillaries, anhydremia, diminished blood volume and poor venous return. There is a close relation between this syndrome and traumatic and anaphylactic shock. The fact that large amounts of histamine are present in the body is another feature which has stimulated research designed to investigate the possibility that histamine is the causative agent in traumatic and allergic shock. It is impossible here to review the voluminous literature on this subject (*see* Best and McHenry, 1931; Dragstedt and Mead, 1937). It may be mentioned that those who maintain that histamine is the causative agent in traumatic shock believe it to be released as a result of extensive tissue damage. Likewise in anaphylactic shock it has been postulated that the intracellular reaction between antigen and antibody injures the cell, leading to a liberation of histamine and other substances.

There is more definite evidence that histamine may be the causative agent in the so-called physical allergies. As an example of physical allergy, sensitivity to cold may be cited. Certain individuals, if exposed to cold, as for example while swimming in cold water, experience anaphylactoid symptoms. These may be severe and can be elicited under carefully controlled laboratory conditions by immersing the extremities in cold water. They consist of vasodilatation, fall in blood pressure and accompanying subjective symptoms. The specific observation which definitely implicates histamine as the causative agent is the increased secretion of a gastric juice of high acidity which accompanies the vascular changes (Brown and Barker, 1936).

Smooth Muscle. *Uterus.* Inasmuch as histamine was first isolated from ergot, its action on the uterus was one of the earliest to be studied. In most species histamine stimulates the isolated organ as well as the uterus *in situ*. The action is a direct one on the myometrium. The human uterus responds markedly to histamine at term and immediately postpartum (Jaeger, 1913). Practical use of this action, however, is excluded by the many undesirable side-actions of histamine.

Bronchioles. Histamine constricts bronchioles by a direct muscular action, as can be shown in isolated perfused lungs; this effect is unrelated to innervation, and is usually uninfluenced by atropine. The susceptibility of different species to this action of histamine varies greatly. As little as 0.1 mgm of the drug causes death in guinea pigs as a result of bronchiolar constriction. Bronchial spasm also occurs in man following the administration of large doses of histamine. Weiss, Robb and Ellis (1932) observed no noticeable effect of histamine on the bronchioles of normal persons, but the drug had a broncho-constrictor action in patients with bronchitis, bronchial asthma, emphysema and cardiac asthma.

Gall Bladder. The isolated gall bladder responds to histamine by contracting. In the intact animal, however, the response is inconsistent. Lueth, Orndoff and Ivy (1929) observed in man that evacuation of the gall bladder occurred only occasionally after the administration of histamine. They believed that this evacuation was due to the action of acid from the stomach entering the duodenum rather than to a direct stimulating effect of the drug on the muscle of the gall bladder.

Glands. *Gastric glands.* Histamine stimulates many of the glands of external secretion but the greatest effect is on the gastric glands. Following the administration of histamine to experimental animals or human beings, a copious gastric secretion results. The gastric juice produced has certain characteristics. It has a high acidity and, although it contains appreciable amounts of pepsin, most investigators agree that histamine acts much more intensely on acid-producing cells than on the cells which elaborate pepsin (Figure 63). The mechanism by which histamine stimulates the gastric glands is not known. It is independent of innervation and an isolated gastric pouch responds as readily as normally innervated gastric mucosa. The local application of histamine solution to the gastric mucosa also produces a secretory response. It is possible that the histamine-induced vasodilatation observable in the stomach is the fundamental cause for the copious secretion in that it brings to the glands a richer blood supply. Other vasodilating secretogogues such as the choline esters also produce an abundant flow of gastric juice but the secretion is of a considerably different character (page 368). The action of histamine on gastric secretion can be only moderately antagonized by atropine (Gray, 1937).

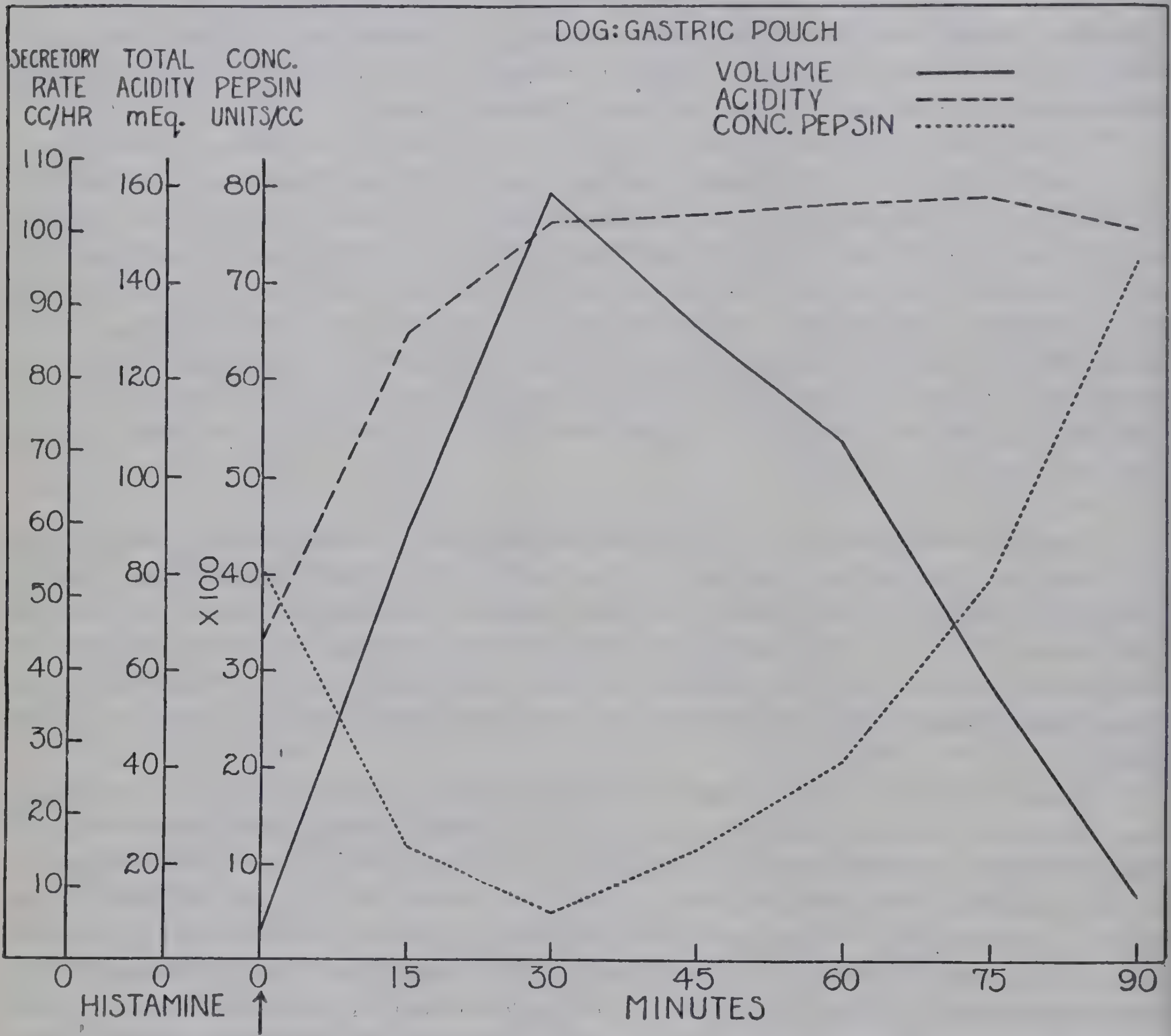


FIGURE 63. *The effect of histamine on the gastric secretion of an isolated stomach pouch in a dog.*

For pepsin unitage, *see* Figure 36. A fasting sample was taken at zero time, after which 0.1 mgm/kg of histamine phosphate was injected subcutaneously, and samples were collected at 15-minute intervals. Note the marked increase in the rate of secretion and the accompanying increase in the total acidity of the gastric juice. Observe also that the concentration of pepsin falls rather than rises. Compare this response with that to carbaminoylcholine shown in Figure 36.

Histamine has been definitely linked with the secretogogue *gastrin,* a substance which can be extracted from the pyloric mucosa and considered by some to be the agent responsible for the secretory activity of the stomach during the "gastric phase" of digestion. Although there is evidence for the existence of such a secretogogue, in all probability the particular substance which can be extracted from the gastric mucosa and which stimulates gastric secretion on injection is histamine. Whether histamine plays a physiological rôle in the production of gastric juice is unknown.

Salivary Glands. Histamine, in experimental animals, stimulates salivary flow when given in comparatively large doses, but the effect is not marked in man. The mechanism of action has not been established. Seemingly the increase in salivary flow is not the result of an increase in blood flow through the glands, for the secretory response far outlasts the circulatory. The action of histamine on salivary secretion has been linked to the cholinergic innervation of the submaxillary gland inasmuch as the response can be potentiated by eserine and abolished by atropine (Gibbs and McClanahan, 1937).

Intestinal Secretions. Histamine stimulates pancreatic secretion to some extent. The action is brief in duration. The drug also stimulates the mucosal glands of the intestinal tract. The mechanism of these actions is unknown but it has been observed that atropine may inhibit the responses.

Absorption, Fate and Excretion. Histamine is rapidly absorbed from all sites of administration. It is only active, however, after parenteral administration. Very little histamine escapes into the urine, most of it being destroyed in the body. There are probably two mechanisms operating in the destruction of histamine. A chemical process, possibly deaminization with subsequent oxidation, probably accounts for the rapid detoxification of parenterally injected histamine. The second mechanism, which is concerned especially with the fate of histamine in the gastro-intestinal tract, has long engaged the attention of investigators. The oral ingestion of histamine in doses which would be toxic if injected causes no symptoms. Furthermore, appreciable amounts of this amine are continually being formed in the intestine. Best (1929) and Best and McHenry (1930) demonstrated that there is an enzyme, histaminase, in animal tissues which is capable of destroying histamine. It is present in highest amount in the intestinal mucosa and in the kidney. Thus it seems that histamine absorbed from the intestinal lumen may be inactivated in the intestinal mucosa.

Histaminase. Histaminase possesses the characteristic properties of an enzyme. Thus it appears to be a protein and it can be inactivated by heat. The enzyme acts but slowly and several hours are required *in vitro* before destruction of the substrate can be demonstrated. So slow is the action that 24 hours are required to assay enzymatic activity, and one unit of histaminase has been designated as that amount which inactivates one mgm of histamine in 24 hours. The enzyme has been marketed for use in the treatment of various allergic disorders in forms suitable for oral or parenteral administration. There is no evidence that histaminase resists destruction in the gastro-intestinal tract.

Toxicology. Histamine poisoning is rare and usually results from an error in dosage. The symptoms are more alarming than dangerous. They consist of a precipitous fall in blood pressure, generalized vasodilatation with a rise in skin temperature, intense headache, visual disturbances, bronchial constriction and dyspnea, a metallic taste, vomiting, diarrhea and, in severe cases, shock. Epinephrine is a specific physiological antagonist to histamine and will prevent or counteract all symptoms if administered quickly. If shock occurs, it is necessary to restore normal blood volume.

Preparations. The pure water-soluble salts of histamine are available. *Histamine Phosphate,* U.S.P., B.P. and *histamine dihydrochloride* are the preparations employed. Both are water-soluble, colorless crystals. *Solution of Histamine Phosphate,* U.S.P., contains one mgm of the drug per cc.

Therapeutic Uses. Histamine would be a more important therapeutic agent if its actions were more selective. It is valuable chiefly as a diagnostic agent for *gastric function tests.* In this regard, histamine has many advantages over a test meal, for it is the most potent stimulant of the secretion of free hydrochloric acid. A test meal causes dilution and neutralization of the gastric contents and thus obscures the chemical composition of the gastric juice. After histamine, not only is the secreted gastric juice obtainable in pure form, but the response of the glands to the drug is not influenced by such factors as appetite, apprehension and other psychic disturbances. Also, histamine is a much more powerful stimulant of hydrochloric acid secretion than is food. By employing histamine one can more readily distinguish between true and pseudo gastric achylia. In order to test the secretory function of the stomach, histamine is usually given after a night's fast. The dose employed is 0.25 to 0.5 mgm. It is injected hypodermically, preferably in an extremity. If a severe reaction occurs or if a mistake in dosage has been made, a tourniquet can then be applied and the rate of absorption adjusted to keep the patient symptom-free. The maximal gastric response to histamine occurs in 20 to 30 minutes, and secretion subsides in one to one and one-half hours.

Histamine has also been employed as an agent for the determination of *circulatory velocity*. In this procedure, histamine (0.1 mgm) is injected into a vein of the arm or leg. When the drug reaches the superficial vessels of the face, a flush is observed. The interval between the injection and the appearance of the flush is a measure of the time required for the blood carrying the drug to circulate from the site of injection to the face. Histamine is seldom used for this purpose because more accurate end-points can be obtained with sodium cyanide, saccharin and other agents.

Mention has already been made of the evidence which points to histamine as the causative agent in *cold allergy*. It is of interest, therefore, that successful treatment of this condition has been reported by desensitization with histamine (Roth and Horton, 1937). In this procedure, increasing doses of histamine are administered in much the same manner as one would give antigen in desensitizing to a foreign protein. The usual initial dose is 0.1 mgm and this is gradually increased to 1.0 mgm. Success in treating physical allergy has also been reported from the use of *histaminase* (Roth and Horton, 1937). Final judgment on both these measures must be reserved until many more cases have been studied.

Allergy other than that of the physical type has been treated with courses of histamine, and some claim to have obtained favorable results. The value of this procedure is far from established. Also extravagant claims have been made for the relief afforded by histaminase in the treatment of diseases of allergy. However, carefully controlled studies (Keeney, 1940; Miller and Piness, 1940) indicate that the preparation is of little or no value in the treatment of allergic disorders, and many experimental observations on the inability of histaminase to prevent the responses to injected histamine support this conclusion.

The vasodilator action of histamine has been employed for various purposes. Administration of histamine by iontophoresis has been employed in the treatment of peripheral vascular disease. The subcutaneous injection of histamine is said to offer symptomatic relief in many cases of *rheumatoid arthritis* (Muether, 1940). The drug has also been incorporated in an ointment base for the local therapy of *indolent ulcers*. Histamine has been tried in *tobacco amblyopia*, but preference should be given to the nitrites and choline esters. Shelden and Horton (1940) reported that patients with *Ménière's disease* respond in a spectacular manner to the slow intravenous infusion of histamine. The typical histamine wheal can be utilized to determine the level of *circulatory competency* in an extremity when operation is contemplated for gangrene, because the appearance of the wheal after the intradermal injection of a 1:1000 histamine solution depends upon an adequate circulation of blood in the finer vessels.

The flare noted around the periphery of the histamine wheal depends upon the integrity of the axon reflexes, that is, upon the functional competence of peripheral sensory nerves. Therefore, provided the circulation is adequate, the intradermal injection of histamine can be employed as a test for certain *neurological disturbances* (Loeser, 1938). These include the differentiation between hysterical and organic cutaneous anesthesia, the detection of malingering, the following of degeneration and regeneration of peripheral sensory nerves, the localization of expanding spinal cord lesions involving the dorsal root ganglia, and the differentiation between peripheral nerve and spinal cord lesions.

THIOCYANATES

(Sulfocyanates, Rhodanates)

Potassium and sodium thiocyanate were introduced into medicine for the symptomatic therapy of essential hypertension, but otherwise these drugs have no medicinal usefulness. Apparently Pauli (1903) was the first to report the efficacy of thiocyanates as a therapeutic hypotensive agent. Due to toxic effects, however, the drug was not widely employed until Westphal in 1925 revived its use.

Chemistry and Preparations. The SCN^- ion is the basis for the pharmacologic effects of thiocyanate salts. The ion does not further dissociate in the body, the atomic linkage being $-S-C{\equiv}N$, and it therefore has no actions in common with cyanide. Indeed, the cyanides are detoxified in the body by conversion to the stable and much less toxic thiocyanate. The sodium and potassium salts of thiocyanate are official in the N.F., which also includes the *Elixir of Sodium Thiocyanate,* a four per cent solution of the drug.

Pharmacological Actions. The thiocyanate ion has two major actions in the body, one similar to that of the iodides and a second like that of the nitrites. For example, it is capable of causing cutaneous and mucosal phenomena characteristic of iodism, and of relaxing smooth muscles as do nitrites. The latter action is the basis for the therapeutic use of thiocyanates in essential hypertension.

Absorption, Fate and Excretion. Thiocyanates are readily absorbed from the intestinal tract. The thiocyanate ion is distributed throughout body fluids in a manner identical with that of chlorides and bromides, that is, extracellularly (Wallace and Brody, 1937). The ion is not oxidized or otherwise altered in the body, and tissue cells are apparently impermeable to it. For this reason thiocyanates can be used to estimate the volume of the *interstitial fluids* of the body. The thiocyanates are excreted from the body mainly by the kidneys but the rate of excretion is variable and unpredictable. This necessitates colorimetric determinations of the serum levels of thiocyanate when the drug is used in man, because the dose cannot be relied upon to serve as an index of safety in medication.

Toxicity. Thiocyanates are not innocuous and a number of deaths have been recorded in the clinical literature from their use in hypertensive patients. These deaths have been analyzed by Wald, Lindberg and Barker (1939). Barker (1936), on the basis of considerable experience with thiocyanate therapy, has correlated the untoward symptoms and toxic effects with the serum level of thiocyanate (*see* also Wald, Lindberg and Barker, 1939). The "safe limit" of serum thiocyanate is considered to be between eight and 14 mgm per cent. At this range, a hypotensive action is manifest but certain mild toxic responses are also noted. At levels above 15 mgm per cent, toxic manifestations of a severe nature may appear.

The *mild reactions* noted in patients with therapeutic concentrations of serum thiocyanate consist of weakness, especially of the arms and legs, fatigue, lethargy, aching and cramping in the calf muscles, increased nervousness and irritability, and symptoms of iodism such as coryza and a toxic dermatitis which may assume the form of a maculopapular itching and scaling eruption. Occasionally, the eruption may be severe and exfoliate and be accompanied by fever, edema of the face and marked intoxication. After prolonged thiocyanate therapy, the thyroid gland may show diffuse benign enlargement. The pathological significance or character of this hypertrophy is not known. Mild gastrointestinal complaints are not uncommon and consist of pyrosis, abdominal pain, vomiting and diarrhea.

Severe reactions to thiocyanates consist of the aforementioned symptoms in an exaggerated form. In addition, vascular collapse may occur. Cerebral manifestations are characteristic and consist of dysarthria, aphasia, confusion, hallucinations, mania and delirium. Cerebral thromboses and anginal pain have also been reported but there is a question whether they can be ascribed etiologically to thiocyanate medication. Coma, convulsions and death occur in the severely poisoned patients. Whether long-continued thiocyanate therapy with maintenance of "safe" blood levels results in chronic poisoning is disputed. Anemia, emaciation, muscular wasting and constant fatigue develop in patients receiving the drug over long periods of time, but Wald, Lindberg and Barker (1939) are inclined to attribute these effects to the progressive nature of the hypertensive vascular disease itself rather than to therapy.

Therapeutic Status. Thiocyanates are employed only in patients with essential hypertension. If used at all, thiocyanate therapy must be accompanied by periodic examination of the serum level of the drug and this level must not be allowed to rise above 12 to 14 mgm per cent. Initial dosage in the average case consists of 0.3 gram daily of the sodium or potassium salt for three days. The maintenance dose needed to obtain hypotensive effects without toxic side-actions varies widely from 0.3 gram weekly to one gram daily, and fluctuates from time to time in the same patient.

The criteria set forth by Weiss and Ellis (page 563) in connection with nitrite therapy of hypertension are clearly not fulfilled by thiocyanates. The drug is toxic and most patients receiving apparently safe doses at times experience untoward effects. Intolerance to thiocyanate cannot be determined in advance. The margin of safety is narrow, the danger of cumulative toxicity ever present, and the therapeutic benefit apparently rests on some degree of toxic action of the drug. Despite the favorable clinical reports which appear from time to time (Wald, Lindberg and Barker, 1939; Massie, Ethridge and O'Hare, 1938; Robinson and O'Hare, 1939) clinical results with thiocyanate on the whole have not been promising. Death has been reported in a patient receiving the drug under observation and with the serum level controlled at a supposedly nontoxic range (Garvin, 1939). The thiocyanates have not been accepted for inclusion in N.N.R. and the Council on Pharmacy and Chemistry has advised against their use. They cannot be generally recommended for indiscriminate employment in therapeutics. One desiring to prescribe the drug should be fully aware of its toxicity, the purely symptomatic nature of the relief afforded, and the necessity of carefully observing the patient and controlling the serum level of the ion.

ACONITE

Historical. Aconite is a very old drug and was used in ancient times as an arrow poison. It is obtained from many species of plants widely distributed throughout the world, the official U.S.P. source being the root of *Aconitum napellus* (wolfsbane; monkshood), a plant often cultivated in gardens.

Chemistry and Preparations. The substance in aconite which accounts for the activity of the drug is an alkaloid, *aconitine,* an unstable acetyl benzoyl ester of a quinoline base. Aconitine cannot be used in medicine due to its instability, and severe poisoning and fatalities have occurred from its administration. *Tincture of Aconite,* U.S.P., is an official preparation and each cc is equivalent in activity to 0.15 mgm of freshly prepared reference *Aconitine,* U.S.P. The dose of the tincture is 0.6 cc. The dose of *Aconite,* U.S.P., is 0.06 gram. Aconite is also available in the B.P., and in the form of an N.F. dental ointment with iodine, an N.F. liniment with chloroform and an N.F. fluidextract.

Actions. Aconite acts both peripherally and centrally on the nervous system. The *peripheral action,* observed even on local application due to absorption of the drug through the skin or mucosa, is mainly sensory and manifests itself in a feeling of warmth, tingling and numbness unassociated with redness or inflammation. Tingling is noted even after oral administration of aconite.

The *systemic effects* of aconite are mainly due to selective stimulation of the central nervous system. The medullary vagal centers are particularly susceptible and their stimulation accounts for the slowing of the heart rate and the fall in blood pressure noted after the administration of aconite. After large doses, central depression occurs.

Poisoning. After toxic doses of aconite, tingling is widespread and very diagnostic. Nausea, emesis, diarrhea and abdominal pain occur. The pulse is weak, blood pressure low, respirations difficult and vision impaired. Death may occur rapidly due to acute cardiac failure. The lethal dose of aconitine is approximately six milligrams. Autopsy findings are not characteristic and the drug is difficult to identify in small amounts. For these reasons, it was a favorite of criminal poisoners. Accidental poisoning may occur from the local application of the drug or from the ingestion of garden plants of the monkshood or larkspur family. Treatment of intoxication is purely symptomatic. Atropine should be used to counteract vagal stimulation.

Uses and Status. Aconite has been used locally for the relief of neuralgia, toothache and similar pains. Due to the possibility of absorption and toxic systemic effects, aconite should not be employed on the surface of the body.

Aconite has also been used systemically in fevers for the depressant effects on the heart, and in hypertension to lower the blood pressure. Both of these uses are dangerous and obsolete, and the drug exerts its effects solely by virtue of its toxic properties. Aconite has deservedly joined veratrum in obsolescence.

VERATRUM

Veratrum Viride, U.S.P., is obtained from the rhizome and roots of the liliaceous plant *Veratrum viride* (green Hellebore). It contains a mixture of alkaloids, the most important of which is *protoveratrine.*

Actions. The main action of veratrum is stimulation of the vagal nuclei in the medulla. This results in a slowing of the heart rate, a fall in systemic blood pressure, and a "collapse reaction" characterized by sweating and reduction in body temperature. Poisoning by veratrum is characterized by nausea and vomiting, diarrhea, headache and cardiovascular collapse. Death, however, is rare because of the rapidity with which large doses of veratrum are vomited.

Use and Status. Veratrum was formerly used as a "cardiac depressant," especially in fevers and in eclampsia. The therapeutic objective was to "slow and soften" the pulse and reduce the body temperature. The drug is practically obsolete today and enjoys a deserved oblivion. The preparation used was *Tincture of Veratrum Viride,* U.S.P., in a dose of one cc every hour for four doses.

Veratrine (Cevadine). Veratrine is a mixture of alkaloids obtained from the seeds of a Hellebore plant, *Veratrum cevadilla.* The alkaloid *cevadine* is the most important constituent. The major pharmacological action of veratrine is on skeletal muscle to produce a characteristic prolonged contracture. This contracture has been the subject of much academic investigation, but has no clinical application. Actions of veratrine on the circulation are quite complex and resemble somewhat those of protoveratrine. Locally, veratrine is a marked irritant and serious poisoning has occurred from its local application for purposes of counterirritation in neuralgia. The drug is dangerous and should not be used clinically.

CACTUS

Cactus Grandiflorus, N.F., the fresh stems of the *Night Blooming Cereus,* is purely of historical interest, having been used in the past as a substitute for digitalis. It is usually available only as a constituent of proprietary medicines, although both the powdered stem and tincture retain their status in the N.F.

Despite its imposing official name, cactus has no demonstrably active pharmacological principle, and there is no experimental or clinical evidence that it has therapeutic value.

A number of other cacti may contain pharmacologically active substances, such as *mescal* (*"peyote"*) obtained from *Laphophora williamsi* (dumpling cactus). Mescal is employed in the religious ceremonies of the Southwestern American Indians for the psychic effects and hallucinations which it produces. A detailed clinical study of the mescaline psychosis has been presented by Stockings (1940), and Castetter and Opler (1936) have reviewed the use of cacti by the Apaches for food, drink and narcotics.

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SECTION VII

WATER, SALTS AND IONS

CHAPTER 32

WATER, SODIUM SALTS AND OTHER AGENTS AFFECTING THE VOLUME AND COMPOSITION OF THE BODY FLUIDS

It is probable that life started in an aqueous environment. A fact often overlooked is that all living matter, even in the highest state of organization, is still totally dependent upon the integrity of a fluid environment. In the process of development, the fluid medium of man has become enclosed within a protective waterproof layer of keratin. This has greatly increased his sphere of activity; but, on the other hand, has burdened him with the maintenance of his body fluids. This does not mean only that a certain amount of fluid must be ingested each day, because there is more to an aqueous environment than water. The concentration of ions in body water must also be adjusted with great accuracy in order that life may continue. Any breakdown in this adjustive mechanism leads to serious consequences that demand corrective procedures with water and salts. The fact that these pharmacological agents are such prosaic substances does not detract from their importance. It is perhaps unfortunate that more attention is paid to the pharmacodynamics of a relatively useless alkaloid, such as strychnine, than to simple yet valuable agents such as water and salts.

The Distribution of Body Water. The importance of water to the organism cannot be overemphasized, and the functions it serves are well known. It is not sufficient that water be present in a definite amount in the body, but also it must be specifically distributed in various compartments. Indeed, it is possible to produce death in animals by altering water distribution without affecting the total water content of the body. *Many of the clinical manifestations of dehydration are the result of altered water distribution rather than water loss.*

Body water can be divided into two main compartments. The water within cells is known as *intracellular water* and accounts for 50 per cent of the body weight. The remainder of the body water is outside of cells. It is known as *extracellular water* and comprises about 25 per cent of the body weight. The *extracellular fluid* reservoir can further be divided into that which is within the circulatory system, the *circulatory fluid,* and the larger portion outside of the circulation known as the *interstitial fluid.*

Factors Which Govern the Distribution of Body Fluid. *Osmotic Pressure.* The distribution of fluids in the body is governed by osmotic forces and, in order to understand the manner in which these forces operate, it is necessary to have a working concept of what is meant by the osmotic pressure of a solution.

For such an understanding, one must start with Boyle's basic law of gases, namely, that the pressure of a gas varies inversely with the volume. Thus the greater the number of molecules of a gas confined to a given space, the greater will be the pressure they exert. This pressure, due to the kinetic activity of the gas molecules, can easily be demonstrated and measured.

In solutions, the molecules of solute and solvent also have a definite kinetic energy. The pressure exerted is known as *osmotic pressure,* and, as is the case with gases, this pressure is directly proportional to the number of molecules of solute per unit of solvent. Unlike the gases, however, the solute and solvent are confined within definite boundaries and the pressure exerted can be measured only under special circumstances, namely, when solutions are separated by a semipermeable membrane.

First, however, consider an aqueous solution of sodium chloride separated from water by a membrane permeable to water and sodium chloride. In the salt solution, there are obviously more molecules of sodium chloride than in the pure solvent. On the other hand, per given volume of fluid, there are more molecules of water in the pure solvent, because in the salt solution the water has been diluted by the presence of salt. When separated by permeable membranes, substances diffuse from areas of high concentration to areas of low concentration, for there are more molecules bombarding the membrane from the side of higher concentration and consequently more get through. Therefore, in the situation cited, water will diffuse into the salt solution and salt will diffuse into the water until the concentrations of all substances are equal. No pressure will develop because all constituents are diffusible.

Now separate the solution of sodium chloride from pure water by a membrane that is impermeable to salt but permeable to water. On one side, there is again a greater concentration of salt molecules, on the other side a greater concentration of water molecules. The salt molecules will bombard the membrane, but due to the fact that they cannot get through they will not diffuse into the pure water. Water molecules will strike the membrane and pass through it from both sides; but, inasmuch as the presence of salt has diluted the water on the side of the solution, more water molecules will bombard and pass through the membrane from the side of the pure water. Water continues to diffuse into the salt solution until the solutions on both sides of the membrane have the same concentration of water molecules, or in other words until the salt solution is infinitely diluted. This passage of fluid is known as *osmosis.*

Suppose now that there is a pressure which opposes the passage of the water across the membrane into the salt solution. For example, construct a system of such a nature that the passage of water into the salt solution will raise a column of fluid which exerts a hydrostatic pressure opposing the entrance of any more water. Then the height to which that column will rise before the pressure is sufficient to stop the unequal passage of water molecules across the membrane is a measure of the osmotic pressure of the salt solution. The word unequal is used advisedly because water molecules are still crossing the membrane in both directions, but now the pressure exerted on the salt solution is sufficient so to increase the activity of the water molecules on that side that the number going through from the salt solution to water is now equal to that passing in the opposite direction. A very simple definition, then, is that *osmotic pressure is the hydrostatic pressure necessary to prevent osmosis. Osmosis may be defined as the diffusion of water through a semipermeable membrane to a site of lower water concentration.*

Lastly, consider an example of a membrane impermeable to all salts and separating a solution of sodium chloride from one of potassium chloride, both solutions having the same molar concentration. Now, inasmuch as the water on each side of the membrane is diluted by the same number of molecules of salt, the concentration of water on each side of the membrane is the same and the molecules of water will diffuse at an equal rate in both directions. In other words, both solutions have the same osmotic pressure and they are known as *isotonic solutions.* Isotonicity is thus completely independent of the particular salts in a solution but is dependent upon the concentration of these salts.

The Regulation of Fluid Distribution by Osmotic Forces. It is now possible to consider how osmotic forces regulate the distribution of body water. As has already been stated, the water compartments of the body can be separated into intracellular and extracellular, and the latter can be further subdivided into the circulatory and interstitial.

The osmotic forces which act to regulate the relative volumes of circulatory and interstitial fluid have been elucidated by Starling. They are well known and will be reviewed briefly. As a first essential for selective fluid distribution, a semipermeable membrane is necessary. In this instance, it is the capillary wall. This membrane is impermeable to serum proteins, but not to water and salts. Therefore the proteins confined within the capillary will exert an osmotic force which attracts fluid from the interstitial spaces into the circulation. Opposed to this force is the hydrostatic pressure of the circulating fluid within the capillary. Thus fluid will leave the capillaries as long as the hydrostatic pressure within these vessels is greater than the osmotic force of the serum proteins, and water will enter the circulation when the opposite is true. This passage of fluid is discussed in detail in the chapter on diuretics (page 643). Inasmuch as the capillary wall is freely permeable to water and salts, the ionic composition of the interstitial fluid is approximately the same as that of the serum.

In connection with the pharmacology of water and salts, however, it is the factors governing the distribution of intra- and extracellular water which are of greater interest. It should first be pointed out that water diffuses readily into all the cells of the body. Therefore, it must follow that all the body fluids are isotonic because water will distribute itself until it has the same concentration everywhere. The amount of water going to any particular site depends upon the concentration of nondiffusible ions or molecules at that site. Nondiffusible substances are those to which membranes are impermeable. It is probably the nondiffusibility of the inorganic cations of the body fluids across cell membranes which controls the distribution of body water to a large extent.

An analysis of animal tissue reveals that the two chief cations are sodium and potassium, and that *most of the cation found in the intracellular fluid is potassium, whereas sodium is the cation of the extracellular fluid.* Thus in human blood, sodium is present in the serum and potassium in the red blood corpuscles. Likewise, in muscle tissue the interstitial fluid contains sodium salts whereas the fluid in the cell contains potassium salts. Obviously the membranes of cells must be impermeable to at least one of these cations, otherwise there would be no such discrete distribution. Evidence indicates that it is the sodium rather than the potassium which cannot traverse the cell wall and this accounts for the specificity of composition of the different body fluids (Winkler and Smith, 1938).

With sodium fixed in an extracellular site, it is apparent that water alone will not enter the cell unless there is a decrease in the concentration of extracellular sodium. Otherwise the cell would become hypotonic to extracellular fluid. Likewise, water cannot leave the cell. Therefore, in the last analysis, *it is the concentration of the sodium ion in the extracellular fluid which largely regulates the degree of cellular hydration.* A major function of the kidney is to guard the concentration of sodium in the extracellular fluid. If the sodium content of the extracellular fluid is raised, water leaves the cell because concentration gradients now exist between intra- and extracellular fluids. Inasmuch as the cell membrane is impermeable to sodium, the passage of water is the only mechanism available to reestablish isotonicity. Conversely, a fall in extracellular sodium concentration causes cellular hydration.

The water and salt intake, the regulatory activity of the kidney, and the osmotic forces exerted across semipermeable membranes all keep the internal environment constant with respect to the degree of hydration and the distribution of body water. This is so accurately accomplished that the osmotic pressure of all body fluids is kept very constant.

The pharmacological properties of water and sodium chloride may now be considered.

WATER

The administration of water causes dilution of all body fluids. When water is taken orally, the sequence of osmotic adjustments is rather complicated. The first ionic equilibration takes place in the intestine. Here the salts of the extracellular fluid can freely enter the lumen of the intestine and water can pass into the capillaries, for the intestinal membrane is permeable to all the constituents being considered. Osmotic equilibration rapidly occurs and all the fluid finds its way into the circulation. Thus water first gains access to the extracellular fluid. This lowers the concentration of sodium and momentarily the osmotic pressure of the fluid outside cells is less than that within cells. An osmotic gradient thus exists and water will pass into cells in order to reestablish isotonicity. The sequence of events following water administration is here depicted in discrete steps. Actually, all changes are occurring simultaneously and as a result there is a rapid and uniform distribution of water throughout the body. At the same time, the regulatory action of the kidney comes into play. The concentration of body electrolytes has been reduced and this is the physiological stimulus for the kidney to rid the body of water and to conserve electrolytes. The efficiency of the kidney in performing this task is evident from the large volume of urine of low osmotic pressure which is formed following the ingestion of copious amounts of water. The mechanism of water diuresis is discussed elsewhere (page 628).

Water Intoxication. If water is absorbed more rapidly than it is excreted, it accumulates in the body and eventually gives rise to toxic symptoms. These result from excessive hydration of body cells. The simplest example of the action of water on cells is seen in the hemolysis of red blood cells.

Hemolysis. When red blood corpuscles are exposed to water, they swell and rupture. Here again passage of fluid is due to osmotic forces. The interstitial fluid of red blood cells is the serum. The cation of the serum is sodium, that of erythrocytes, potassium. (Several species, among them the dog and pig, have sodium in their red corpuscles, potassium in all other cells.) The membrane of the red blood cell is impermeable to the sodium ion, and when water dilutes the external environment the difference in osmotic pressure which exists between the exterior and interior of the cell leads to a passage of water through the cell membrane. This influx of fluid causes cellular swelling which eventually leads to rupture of the cell membrane and escape of the cellular contents.

Cellular Hydration. With excess body hydration, all body cells swell in a similar manner. Cells of organized tissues mechanically support each other, however, and the cell membranes remain intact. Marked pressure changes probably occur due to this cellular turgor and lead to a syndrome called "water intoxication." This has been extensively studied especially by Rowntree (1926). Muscle tremors, cerebral edema, and convulsions are prominent symptoms. Hemoglobinemia and hemoglobinuria also occur because of hemolysis of red blood cells. Indeed, water retention induced by large amounts of the antidiuretic principle of the posterior pituitary may lead to severe hemolytic anemia (Gilman and Goodman, 1936). A mild degree of water intoxication not infrequently occurs in human beings. It usually results from the ingestion of excessive amounts of water combined with a loss of salt.

Water Loss. The loss of body water is even more serious than a plethora of water, because the body cannot lose much of its fluid without fatal results. Extracellular water is continually being dissipated by evaporation from the cutaneous and pulmonary surfaces of the body and by excretion through the kidneys. If this fluid is not replenished, the concentration of extracellular electrolyte increases and this in turn draws water from the cells. This type of dehydration, therefore, eventually depletes the fluid of all body compartments. However, one of the important functions of the kidney is that of regulating the concentration of extracellular electrolyte. Therefore, when the concentration of the latter is raised due to dehydration, some of the "excess" electrolyte is excreted. In this manner, the kidney preserves cellular water because with the excretion of sodium less intracellular fluid has to be withdrawn to maintain osmotic equilibrium. This adjustment is therefore accomplished chiefly at the expense of extracellular fluid and is reflected in an anhydremia. Actually, in simple dehydration, water loss exceeds the excretion of electrolytes and the body in general is depleted of fluids.

Clinically, dehydration is usually accompanied by varying degrees of electrolyte depletion. Before discussing conditions of clinical dehydration, it is necessary to consider the pharmacology of sodium, the cation of the extracellular fluids.

SODIUM

In a certain sense, sodium is pharmacologically inert. Being the cation of the extracellular fluid, it is present in the body in large amounts and apparently its function is purely an osmotic one because it has no specific effect on tissues. Nevertheless, the physical rôle which it plays is important and any change in sodium concentration in body fluid leads to serious disturbances characterized by abnormal fluid distribution.

Effects of Isotonic Sodium Chloride Solution on Fluid Distribution. When isotonic sodium chloride solution is given, either orally or parenterally, it is distributed in a much different manner than water. The presence of the sodium ion in the administered fluid in the same concentration as it is normally present in the body precludes the possibility of any of the fluid penetrating into the cell. This is because the cell membrane is impermeable to sodium and no osmotic gradient exists to permit the passage of water. Thus an *isotonic sodium chloride solution remains extracellular in its distribution.* This fact can easily be demonstrated. If on different occasions equal volumes of isotonic sodium chloride solution and water are given to an individual, the extracellular fluids, as exemplified by the circulation, will be diluted to a much greater extent by the salt solution than by the water. The extent of dilution can be measured by the simple procedure of hemoglobin determination. The kidney, however, soon readjusts the increased volume of extracellular fluid to normal, for this organ regulates the total volume as well as the composition of the extracellular fluid. It accomplishes this by the excretion of both sodium chloride and water. The mechanism of sodium chloride diuresis is discussed on page 628.

When sodium salts and water are lost from the body in isotonic proportion, as for example in diarrhea, the situation described above is reversed. Of paramount importance is an appreciation of the fact that the osmotic pressure of the body fluids is not altered by such a loss. Although the total amount of extracellular fluid is diminished, the electrolyte concentration and hence the osmotic pressure of the remaining fluid is unchanged. Consequently, the body cells are still in osmotic equilibrium with their extracellular environment and therefore cannot contribute any of their fluid to make up for this deficit, because no osmotic force exists to cause such a shift in water distribution. All compartments of the extracellular fluid reservoir will be depleted. The diminished circulatory blood volume accounts for most of the symptoms encountered in this type of dehydration.

The loss of extracellular fluid is the most common cause of clinical dehydration. In itself it is serious, but in addition it is often complicated by a disturbance in the acid-base balance. Acid-base disturbance occurs when the fluid lost contains a predominance of a single anion, such as the loss of bicarbonate (HCO_3^-) during diarrhea. This will be discussed more fully below.

Effect of Hypertonic Sodium Chloride Solutions on Fluid Distribution. The administration of hypertonic sodium chloride solution leads to a greater distortion in the distribution of body fluids than when an isotonic solution is used. The concentration of extracellular cation is raised, and the resultant osmotic gradient between the fluids inside and outside the cells can only be removed by the passage of water out of the cell, for the sodium ion cannot gain entrance into the cell. Not only is the extracellular fluid reservoir increased, but the cells become dehydrated. Once this has occurred, there are only two ways in which the fluid content of the cell can be restored to normal. Either the kidney must excrete sodium chloride in excess of water to a degree determined by the hypertonicity of the solution which was administered, or additional water must be taken in order to allow for hydration of the body cells back to their normal water content. The kidney can so concentrate sodium salts that they appear in the urine in approximately twice the concentration of that in the blood (approximately 300 mEq of urinary sodium). Theoretically, if the concentration of sodium administered exceeds 300 mEq, normal body hydration can be restored only by taking water. Thus the drinking by shipwrecked individuals of sea water which has a sodium concentration of approximately 450 mEq can only serve to intensify any existing dehydration.

The Effect of Sodium Loss on Fluid Distribution. A decrease in the sodium concentration of the body fluids leads to an unusual and incapacitating type of fluid distribution. It was previously pointed out that the administration of water decreased the concentration of extracellular sodium and this led to a passage of water into the body cells. In such an instance, the volume of both the intra- and extracellular fluid compartments was increased. If sodium concentration is diminished not by an addition of water but rather by a sodium loss, the resulting situation is much more serious. Once again the extracellular fluid is hypotonic to the intracellular fluid. Osmotic equilibration results in a passage of water from outside to within the cell. In this case, however, the gain in cellular water is entirely at the expense of the circulating and interstitial fluid. As a result one has the bizarre situation in which the body cells are hydrated coincident with anhydremia and extracellular dehydration. The only way in which such a condition can be corrected is by the administration of sodium salts.

Clinical Conditions Characterized by Redistribution or Loss of Extracellular Fluid and Their Treatment

It is now possible to consider those clinical conditions characterized by a disturbance in volume or distribution of extracellular fluid. For convenience of discussion, they are classified into three main groups: (1) conditions unaccom panied by a change in the chemistry of the extracellular fluid but chiefly characterized by its redistribution; (2) conditions characterized primarily by a decrease in the sodium content of the extracellular fluid and an internal shift of water; (3) conditions characterized by a disturbance in acid-base balance. It is important to remember that all these disturbances are primarily concerned with the shift or loss of fluid containing the sodium ion. In replacement therapy, it is necessary to include sodium salts, otherwise the condition being treated will be aggravated.

Preparations Employed in Therapy of Clinical Dehydration. In the following discussion of clinical dehydration, the therapeutic procedures used in treatment will be outlined briefly. Therefore a preliminary consideration of the solutions employed and their method of administration is necessary.

Route of Administration. In correcting a deficit of extracellular fluid one can give replacement therapy either orally or parenterally. In most instances, the latter route of administration must be employed. In many cases fluid loss has resulted from vomiting or diarrhea and little can be gained by oral medication. Dehydration arising from other causes is also often accompanied by vomiting. Lastly, dehydration may be complicated by shock and the administration of fluid by mouth frequently is not feasible. The routes most commonly employed are the hypodermic and intravenous. Often both are used simultaneously. When large volumes must be injected, venoclysis is preferable to hypodermoclysis.

In parenteral therapy, strict asepsis must be observed. The problem of asepsis is complicated by the difficulty attending the sterilization of bicarbonate solutions, and for this reason considerable attention has been given to the whole question of salt solutions suitable for parenteral injection. The various solutions available and the methods employed for their preparation will be described.

Sodium Chloride, U.S.P., B.P. A solution of this salt is the simplest for parenteral administration. *It is the fluid of choice in any case of dehydration uncomplicated by acidosis.* The concentration usually employed is 0.9 per cent, which is isotonic with normal body fluids. It may be sterilized by boiling.

Sodium Bicarbonate, U.S.P., B.P. *Solutions of this salt are used to counteract acidosis.* Upon boiling, a solution of sodium bicarbonate liberates carbon dioxide and sodium carbonate is formed, making the solution dangerous to inject. Therefore such solutions cannot easily be sterilized. As an alternative, one can sterilize bicarbonate solutions in sealed ampules. A simple procedure and one that has proved safe is to dissolve sodium bicarbonate (C.P.) in sterile warm water, the transfer from reagent bottle to solution being made with a flamed spatula. No infections have attended the intravenous administration of solutions made in this manner. Another procedure is to boil the bicarbonate solution and then pass carbon dioxide through the sterile preparation until the solution is orange to phenol red. Several substitute solutions have been offered to avoid the difficulties cited.

Sodium Lactate. Sodium lactate is often used instead of sodium bicarbonate. After injection, the lactate ion is metabolized and the sodium combines with bicarbonate available from tissue oxidation. Sealed sterile ampules of molar sodium lactate solution are available commercially. A molar solution of sodium lactate (1000 mEq) is diluted with sterile distilled water to the strength desired (isotonic = 155 mEq). Sodium lactate can be sterilized simply by boiling.

Hartmann and associates (1938) have shown that the levorotatory sodium lactate is metabolized more quickly than the dextrorotatory isomer and thus supplies sodium more readily. The available commercial solutions, however, are those of the racemic salt (sodium r-lactate).

Darrow's Solution. This solution contains a mixture of sodium chloride and sodium bicarbonate. It thus supplies sodium and the two most important anions of the extracellular fluid, and *is of value not only in the replacement of extracellular fluid but also in correcting existing acidosis.* It is prepared by mixing sterile solutions of sodium carbonate and hydrochloric acid in the proper proportions, the details of which are described by Cunningham and Darrow (1931).

Lactate-Ringer Solution. This is one of the most complete solutions for parenteral injection. It contains sodium lactate as well as cations of the extracellular fluid other than sodium. The composition of this fluid per liter is sodium chloride, 6.0 grams, sodium lactate, 2.7 grams, potassium chloride, 0.4 gram, and calcium chloride, 0.2 gram. This solution is employed when it is likely that other important cations as well as sodium have been lost from the body, as for example in severe diarrhea. Sodium bicarbonate may be substituted for sodium lactate in the formula but the solution must then be sterilized in sealed ampules.

Acacia. Acacia and glucose solutions are used in the treatment of body fluid disturbances not primarily for the replacement of extracellular fluid and electrolytes but rather to increase the circulatory volume, especially in the therapy of circulatory shock. The treatment of this condition demands the administration of substances capable of functionally replacing the large amounts of serum which escape from the circulation through injured capillaries. Solutions of acacia may be employed for this purpose. The dangers attending the use of acacia solutions and the preparations available are described under diuretics. In the treatment of shock, acacia should be given as a six per cent solution in isotonic sodium chloride.

Glucose. Glucose solutions are frequently administered in the treatment of dehydration. Although sodium salts are the basic therapy of this condition, glucose performs a variety of functions as follows: (1) The injection of hypertonic glucose solutions is of value in shock in that fluid is temporarily attracted into the circulation. (2) Glucose is antiketogenic and is used in the treatment of ketosis. (3) Dehydration is often accompanied by persistent vomiting and the injection of glucose is a source of food for the patient. (4) The injection of glucose solutions provides a means for the parenteral administration of water unaccompanied by salts. The removal of glucose from the circulation by oxidation leaves a water residue.

Glucose may be given intravenously in isotonic or hypertonic solution. A concentration of 5.5 per cent is approximately isotonic with normal body fluids. Hypertonic solutions as strong as 50 per cent are injected for the purpose of attracting fluid into the circulation or dehydrating cells. Hypertonic solutions should always be given intravenously. Although isotonic solutions of glucose are often given by subcutaneous injection there are two disadvantages (Darrow, 1940). Such solutions are irritating to tissue. Of greater consequence, however, is the fact that a glucose solution in subcutaneous depots will equilibrate in respect to ionic composition with the extracellular fluid before it can be absorbed. The extracellular fluid is thus temporarily deprived of the sodium ion, and this leads to a further distortion in the chemistry and distribution of extracellular fluids (Darrow and Yannet, 1935).

Abnormal Distribution of Extracellular Fluid. A marked alteration in the *distribution* of extracellular fluid between its two compartments, the circulatory and interstitial, characterizes several clinical syndromes. This altered distribution invariably involves the loss of circulatory fluid into the interstitial spaces. As has been stated, fluid remains in the circulation because the capillary walls are impermeable to protein, which exerts an osmotic force attracting fluid from the interstitial spaces. Any disturbance in this mechanism may have deleterious effects on the organism.

Chronic Edema. Edema is an abnormal collection of extracellular fluid in the tissue spaces. The source of this fluid is the circulation. The factors leading to edema formation and the treatment of this condition are described under the clinical use of diuretics (page 643). In chronic edema, fluid is lost only slowly from the circulation. Consequently, there is ample time for its replacement from dietary sources, and the circulatory volume therefore does not suffer. Treatment is centered on ridding the body of this excess interstitial fluid either by correcting the condition causing the edema or by stimulating the renal excretion of extracellular fluid by means of diuretics.

Shock. A sudden change in the permeability of the capillaries leads to a rapid loss of a protein-containing fluid from within the confines of the circulatory system. This condition may be termed acute edema. It differs from chronic edema in that the loss of fluid from the circulation occurs so rapidly that the restorative processes of the body which operate in chronic edema to help maintain an adequate circulatory blood volume have not time to function. The clinical syndrome which results is known as *shock.*

Increased capillary permeability can arise from a variety of causes, clinical and experimental. These may be classified into four main groups: (1) Severe trauma may lead to widespread capillary dilatation. The mechanism of this action is not known, although the release from injured tissue of a histamine-like substance has been postulated. (2) Many drugs and toxins may be directly injurious to the capillary wall. (3) Any process which leads to tissue anoxia may result in extensive alteration in capillary permeability. (4) Severe anaphylactic reactions may produce extensive capillary dilatation. In many instances, more than one of these mechanisms may be operating at the same time. For example, the shock attending an acute severe infectious disease such as pneumonia may be the combined result of tissue anoxia from circulatory failure and respiratory embarrassment, and the action of toxins directly on the blood vessels. The shock which characterizes the toxic action of hypnotics and narcotics may be the combined result of a direct depressant action of the drug on the capillaries combined with tissue anoxia from central respiratory and vasomotor depression.

Regardless of the mechanism by which the capillaries are damaged, a definite sequence of events takes place. Moon (1938, 1940) has contributed greatly to our knowledge of the pathogenesis of the shock syndrome. Once protein has traversed the capillary wall and attains an appreciable concentration in the interstitial fluid, one of the chief mechanisms for the maintenance of the blood volume has been disturbed. Despite the fact that the concentration of serum protein may rise due to hemoconcentration, the presence of protein on both sides of the capillary membrane reduces the osmotic gradient referable to protein between circulatory and interstitial fluid. The effective colloidal osmotic (oncotic) pressure of the blood is diminished and the mechanism for the maintenance of blood volume is thus impaired. Fluid rapidly diffuses from the confines of the circulatory system and the relative volume of the cellular elements of the blood rises. Not only is blood volume reduced but also the blood becomes so viscous as to produce another impediment to the circulation. Briefly, then, the basic condition in shock is an inadequate volume of circulating blood in a vascular system of abnormally large capacity due to peripheral vasodilatation. This results in an inefficient circulation and the carriage of oxygen to the tissues is inadequate. The resulting tissue anoxia, which in itself can be the major cause of shock, intensifies and perpetuates the condition, and establishes a vicious cycle (Figure 64).

In the face of an inadequate circulation, compensatory mechanisms operate in an attempt to maintain blood pressure. There is a general discharge of the sympatho-adrenal system. The heart, which is unimpaired in shock, beats at a rapid rate, but the force of contraction is weak because the inadequate venous return results in poor diastolic filling of the ventricles. Reflex peripheral vasoconstriction is ineffective. The damaged capillaries do not respond to stimuli and arteriolar constriction only aggravates further the reduced peripheral blood flow and tissue anoxia. Consequently, the blood pressure falls to very low levels.

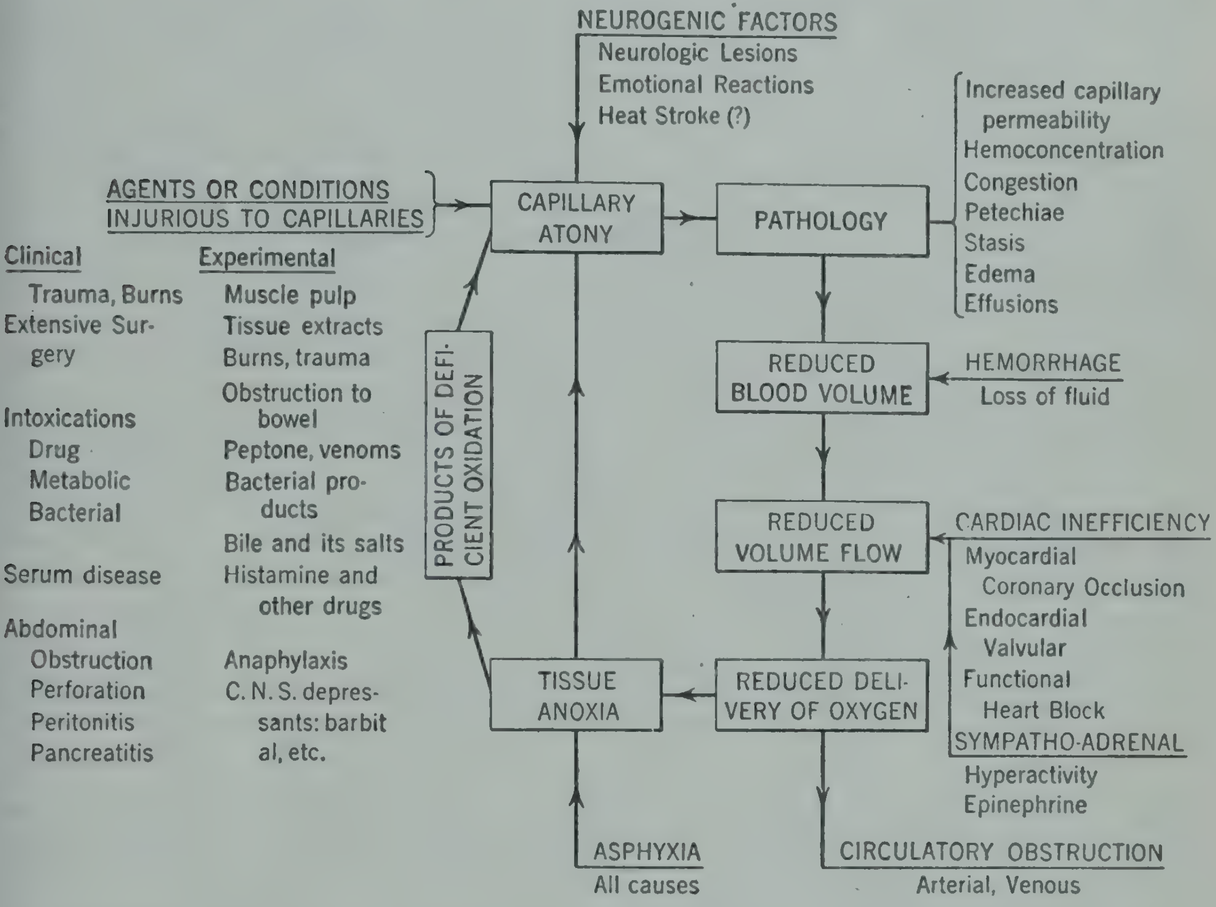
NEUROGENIC FACTORS
Neurologic Lesions
Emotional Reactions
Heat Stroke (?)
Increased capillary permeability
Hemoconcentration
Congestion
Petechiae
Stasis
Edema
Effusions
AGENTS OR CONDITIONS INJURIOUS TO CAPILLARIES
CAPILLARY ATONY
PATHOLOGY
Clinical
Trauma, Burns
Extensive Surgery
Intoxications
Drug
Metabolic
Bacterial
Serum disease
Abdominal
Obstruction
Perforation
Peritonitis
Pancreatitis
Experimental
Muscle pulp
Tissue extracts
Burns, trauma
Obstruction to bowel
Peptone, venoms
Bacterial products
Bile and its salts
Histamine and other drugs
Anaphylaxis
C. N. S. depressants: barbital, etc.
PRODUCTS OF DEFICIENT OXIDATION
REDUCED BLOOD VOLUME
HEMORRHAGE
Loss of fluid
REDUCED VOLUME FLOW
CARDIAC INEFFICIENCY
Myocardial
Coronary Occlusion
Endocardial
Valvular
Functional
Heart Block
SYMPATHO-ADRENAL
Hyperactivity
Epinephrine
TISSUE ANOXIA
REDUCED DELIVERY OF OXYGEN
ASPHYXIA
All causes
CIRCULATORY OBSTRUCTION
Arterial, Venous

FIGURE 64. *Diagrammatic representation of the causative factors and pathogenesis of shock and the vicious circle which ensues.* (After Moon, 1938. Courtesy of the Oxford University Press.)

Additional signs and symptoms characterize shock. The respiration is shallow and rapid. The facial expression is often pinched and anxious. The skin is pale, cold, clammy and often cyanotic. Body temperature falls. The patient is anuric because of the low blood pressure.

Treatment. There is no inherent physiological mechanism by which the other compartments of the body fluids can help to restore the volume of the circulation in shock. An anhydremia exists, but the fluid lost from the circulation is isotonic with other body fluids and therefore no osmotic forces are available to cause any fluid shift from the cells to aid the circulation. The presence of protein in the interstitial fluid tends to fix fluid at that site. Therefore, therapy must be instituted and this is directed toward maintaining an adequate circulating blood volume and effecting a redistribution of fluid back into the circulation. At the same time, however, every effort should be made to relieve the initial cause of the syndrome.

There are many solutions used to restore the blood volume. A large transfusion of blood is the ideal procedure for restoring blood volume and should be used whenever possible, especially when shock is due to blood loss through hemorrhage. This requires time and expense, however, and more available measures are therefore necessary for emergency use. An isotonic solution of sodium chloride may be injected intravenously, but this is only of temporary benefit because the fluid escapes rapidly from the confines of the injured circulatory system. Of more lasting value is hypertonic sodium chloride solution. Because this solution is hypertonic to the fluids outside of the confines of the circulatory system, it will attract extracellular fluid into the circulation by osmotic force. The effect, however, is only short-lived and once osmotic equilibrium has been attained, fluid will once again escape. When employed, hypertonic sodium chloride is best given as a 1.5 per cent solution. It is slowly injected by vein. One or two liters may be administered, but it must be kept in mind that this procedure will dehydrate cells and eventually water must be administered to correct the dehydration. Hypertonic glucose solution is of greater value in restoring the fluid volume of the blood. Glucose is a less mobile molecule than sodium chloride and therefore tends to remain in the circulation for a longer period of time. The osmotic effect of from 10 to 50 per cent glucose solutions is sufficient to attract large amounts of fluid into the circulation. Furthermore, the injection does not cause permanent dehydration, for the glucose is largely removed from the circulation to form glycogen, thus leaving a water residue. An injection of 50 cc of a 50 per cent solution of glucose may be followed by larger amounts of five per cent glucose in isotonic sodium chloride solution, given as a continuous intravenous drip at the rate of from two to 10 cc per minute.

A procedure which is physiologically sound is to augment the colloidal osmotic pressure of the serum by the injection of substances of high molecular weight which will not penetrate the capillary membrane because of their size. Such a substance is acacia. Acacia is usually given as a six per cent solution in 0.9 per cent sodium chloride solution. Five hundred cc can be slowly administered intravenously at one time and the injection repeated in a few hours if necessary. Special purified preparations suitable for intravenous administration should be employed, otherwise serious reactions may occur (page 634).

It is tempting to treat a patient in shock with cardiovascular stimulants. The nature of the shock syndrome, however, dictates against such a procedure. Cardiac stimulants are of no avail for the heart muscle is unimpaired. In fact, the heart responds fully to the reflex stimuli arising from an inadequate circulation, and only requires a greater venous return of blood in order to maintain an efficient circulation. Likewise, it is not feasible to give vasoconstrictor agents. The capillaries are widely dilated due to injury, and circulatory reflexes and the discharge of epinephrine have already caused as much compensatory vasoconstriction as the injured vessels are capable of manifesting. Furthermore, the arterioles are also reflexly constricted in an attempt to maintain the blood pressure. Epinephrine or other vasoconstrictor agents cause a further decrease in peripheral blood flow and aggravate the tissue anoxia. Indeed, Freeman (1933, 1936) believes that arteriolar constriction of sympathetic origin may be a major factor in the etiology of the shock syndrome. For these reasons the administration of epinephrine, ephedrine or pituitrin is useless and may even be harmful. The circulation can only be restored to normal if an adequate blood volume is maintained over a period of time sufficient to relieve tissue anoxia and allow restoration of capillary tone. At the same time, the basic cause for the shock must be removed.

Additional measures employed in the treatment of shock include the use of morphine sulfate if the patient is restless or in pain. The alkaloid should not be given to patients who are quiet and there is a real danger of seriously depressing respiration by the injudicious use of morphine in shock. The patient must be kept in bed and the use of a head-low posture will assist somewhat in aiding venous return and facilitate the maintenance of an adequate blood supply to the brain. Blankets and hot water bottles aid in conserving body heat. The inhalation of oxygen may be beneficial.

Extracellular Fluid Loss Associated with a Decrease in Sodium Concentration and an Internal Shift of Water. *Excessive Sweating.* Body sweat contains appreciable amounts of sodium chloride. This fluid is hypotonic, however, and after copious sweating the body loses proportionately more water than sodium chloride. The changes in blood chemistry and in body water distribution which follow are easily predictable. The water content of the extracellular fluid reservoir is diminished and the concentration of sodium is raised. As a result, water is abstracted from the cells. The final picture is one of a generalized dehydration characterized by anhydremia and cellular water loss. Due to the fact that both sodium and water are lost from the body, the cells are not deprived of fluid to the same extent as is the extracellular compartment. This is because the loss of water and sodium has caused less change in the composition of the extracellular fluid than if water alone had been removed. To clarify this point, if sweat were isotonic in composition, no osmotic change would accompany the loss of this fluid and therefore the cells could contribute no water to help restore the depleted extracellular fluid. In order to restore normal fluid distribution and chemistry, it is only necessary to administer both salt and water in the same proportion in which they were lost in the sweat.

After excess sweating, one is conscious of thirst and usually drinks an amount of water which is roughly proportional to the volume of fluid lost through sweating. This succeeds in restoring the total body fluid volume to normal; but, inasmuch as the sodium deficit has not been corrected, fluid distribution will be further affected. The ingested water distributes itself throughout the fluid media of the body. The cells now receive a larger amount of water than they originally lost by contributing to the extracellular fluid deficit. Conversely, the extracellular compartment retains less of the ingested water than would be necessary to replace the fluid lost in the sweat. The end-result is now a condition of cellular hydration accompanied by a deficit of fluid in the extracellular reservoir. The events leading to such an abnormal distribution of body water are diagrammed in Figure 65. Excess hydration of cells also occurs in water intoxication and many of the symptoms of sodium deficiency from water ingestion after excess sweating are not unlike the early symptoms of experimental water intoxication.

A detailed description of the symptoms of sodium deficiency in man has been given by McCance (1936, 1938). This investigator has produced experimental sodium deficiency in humans by inducing copious sweating and then keeping his subjects in a state of chronic sodium depletion by restricting the dietary salt intake. Fluids were given *ad libitum* and by this means the same type of abnormal water distribution as has been described was obtained. The changes in the blood were all indicative of a loss of extracellular fluid. There was a rise in red blood cell count, hemoglobin, red blood cell volume and plasma protein. Accompanying these changes there was a marked decrease in the concentration of serum sodium.

Definite signs and symptoms were observed. The temporal areas and cheeks appeared sunken and the eyes tired and shrunken. The sense of taste was blunted. Anorexia and nausea were marked. Water metabolism was abnormal, and after the ingestion of large amounts of fluid, diuresis was delayed for many hours. Muscle cramps occurred and any muscle brought into action was liable to manifest spasm. This was especially marked in the fingers. Fatigue and a sense of exhaustion were constant. In addition, mental faculties were dulled and several subjects claimed that they felt "slow in the head." The administration of sodium salts soon restored these individuals to normal.

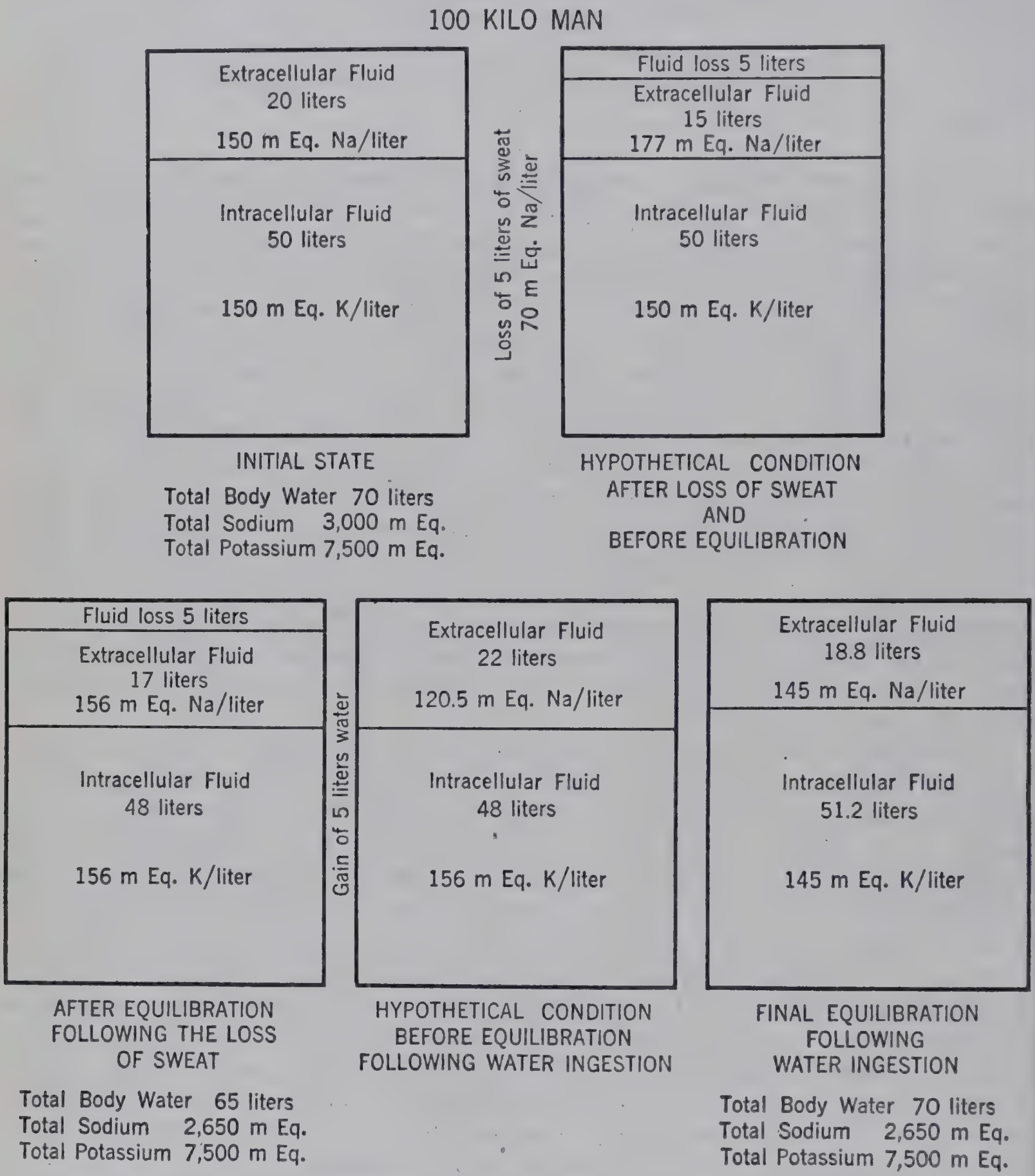
100 KILO MAN
Extracellular Fluid
20 liters
150 m Eq. Na/liter
Intracellular Fluid
50 liters
150 m Eq. K/liter
Loss of 5 liters of sweat
70 m Eq. Na/liter
Fluid loss 5 liters
Extracellular Fluid
15 liters
177 m Eq. Na/liter
Intracellular Fluid
50 liters
150 m Eq. K/liter
INITIAL STATE
Total Body Water 70 liters
Total Sodium 3,000 m Eq.
Total Potassium 7,500 m Eq.
HYPOTHETICAL CONDITION AFTER LOSS OF SWEAT AND BEFORE EQUILIBRATION
Fluid loss 5 liters
Extracellular Fluid
17 liters
156 m Eq. Na/liter
Intracellular Fluid
48 liters
156 m Eq. K/liter
Gain of 5 liters water
Extracellular Fluid
22 liters
120.5 m Eq. Na/liter
Intracellular Fluid
48 liters
156 m Eq. K/liter
Extracellular Fluid
18.8 liters
145 m Eq. Na/liter
Intracellular Fluid
51.2 liters
145 m Eq. K/liter
AFTER EQUILIBRATION FOLLOWING THE LOSS OF SWEAT
Total Body Water 65 liters
Total Sodium 2,650 m Eq.
Total Potassium 7,500 m Eq.
HYPOTHETICAL CONDITION BEFORE EQUILIBRATION FOLLOWING WATER INGESTION
FINAL EQUILIBRATION FOLLOWING WATER INGESTION
Total Body Water 70 liters
Total Sodium 2,650 m Eq.
Total Potassium 7,500 m Eq.

FIGURE 65. *Schematic representation of the effects of sweating and the subsequent ingestion of water on the distribution of fluid and electrolyte in man.* See text for explanation.

Heat Cramps (Miners' Cramps). This is a form of sodium depletion which is observed clinically. It occurs when persons performing hard physical labor in a hot environment sweat copiously, lose large amounts of sodium salts, and then replenish their fluid loss with water. The water shifts which take place have already been discussed. The predominant symptom is muscle cramps which may be so severe as to incapacitate the individual. Spontaneous fibrillary muscle twitchings may accompany these cramps. This syndrome may be rapidly relieved by the administration of sodium chloride. Preventive therapy, however, is far better. If individuals whose work is of such a nature that they perspire copiously are given tablets or solution of sodium chloride rather than water all symptoms may be prevented. The salt concentration in the drinking water need only be as high as in the perspiration, and thus a beverage containing one-half per cent of sodium chloride is sufficient to prevent heat cramps from developing. The subject of heat cramps has been reviewed by Talbott (1935).

Addison's Disease. Adrenal cortical insufficiency is characterized by a functional renal defect which allows the escape of sodium to such a degree that its concentration in the extracellular fluids falls. This by no means is the only physiological disturbance in Addison's disease, but apparently the loss of sodium is responsible for many of the symptoms. McCance (1936) noted that many symptoms of experimental sodium deficiency simulate those of adrenal insufficiency. A sodium loss through the kidneys sufficient to cause a fall in extracellular sodium concentration results in an altered fluid distribution similar to that described, as studies of patients with Addison's disease have shown. It is not possible accurately to determine the degree of cellular hydration, but the anhydremia is evident from the low blood volume and high hemoglobin and serum protein concentrations which characterize this disease. Furthermore, the administration of sodium salts will improve the condition of patients with Addison's disease and of adrenalectomized animals. In fact, one of the diagnostic tests for adrenal insufficiency is to restrict dietary sodium chloride. An intensification of symptoms is strong evidence that the patient is suffering from adrenal cortical insufficiency and that sodium loss is responsible for many of the symptoms of the disease.

Sodium chloride has been extensively employed in the treatment of adrenal insufficiency. It improves the condition of the patient and also decreases the requirement for adrenal cortical extract which is the specific therapy for this disorder. Sodium chloride is usually given orally in tablets in amounts of from 10 to 20 grams daily. (*See* adrenal cortical hormone.)

Extracellular Fluid Loss Complicated by a Disturbance in Acid-Base Equilibrium. The loss or redistribution of body water is often complicated clinically by a disturbance in acid-base equilibrium. The two chief anions of the extracellular fluid are chloride and bicarbonate. If large amounts of chloride are lost from the body, alkalosis results. If large amounts of bicarbonate escape, an acidosis occurs. Therapy necessitates not only the restoration of extracellular fluid but also the correction of deviations from the normal ionic pattern of this fluid.

Under normal conditions, the kidney is capable of maintaining the constancy of composition of the body fluids. The material required for this renal function need be no more than sodium chloride, for a supply of bicarbonate ions is constantly provided by tissue combustion. An excess of a particular anion can be excreted in combination with ammonia. For example, in dehydration resulting from severe diarrhea, fluid of extracellular source is lost through the intestinal tract. It is an alkaline fluid containing a higher concentration of sodium bicarbonate than is present in the circulation and interstitial fluid. Consequently, the extracellular fluid is not only depleted in volume, but the concentration of bicarbonate is reduced and that of chloride augmented.

The symptoms which result are those of dehydration and anhydremia accompanied by acidosis. Fluid and salts must be administered to correct this condition. The fluid must contain sodium in isotonic concentration for the administration of water alone would lead to a condition no different than that described under Miners' Cramp. The question arises whether to give bicarbonate in order specifically to replace the deficit of this anion. Bicarbonate replacement is not absolutely necessary. It is true that isotonic sodium chloride administration will tend still further to intensify the acidosis, for one is giving a higher concentration of chloride than is normally present in the body. However, by restoring base and sufficient fluid to insure an adequate circulation to the kidney, the adjustive mechanisms of the body can now function adequately. The kidney excretes the excess chloride, mainly in combination with ammonia, and the fluid composition of the body returns to normal. On the other hand, one can spare the kidney this task by administering sodium bicarbonate, or substances which are potentially alkaline. The decision depends upon the functional state of the kidney and the severity of the acidosis. In most instances, the administration of sodium chloride in isotonic solution is sufficient. However, there are occasions in which alkaline solutions should be employed. If the acidosis is sufficiently severe to cause hyperpnea, this is the indication, according to Darrow (1940), for the administration of sodium bicarbonate or sodium lactate. Under such a circumstance, it is advisable immediately to correct the acidosis rather than to rely upon renal function, as must be done if only sodium chloride is administered. The dose of sodium bicarbonate or lactate is determined by the degree of acidosis. This can only be ascertained by analysis of the patient's blood. If the carbon dioxide content of the serum is known, the following formula may be used for calculating the intravenous dose of sodium bicarbonate or lactate necessary to correct the existing acidosis (Hartmann and Senn, 1932):

$$\text{mM} = \frac{(60 - \text{CO}_2) \times 0.7\text{W}}{2.24}$$

mM = millimols of sodium bicarbonate or sodium lactate.
CO_2 = serum carbon dioxide content in volumes per cent.
W = body weight in kilograms.
1mM of sodium bicarbonate = 0.084 gram.
1mM of sodium lactate = 1 cc of molar sodium lactate solution.

As an example of how this formula is applied, consider the case of an acidotic individual weighing 60 kilograms with a serum carbon dioxide content of 40 volumes per cent. In order to correct this acidosis, the patient should receive $\frac{(60-40)}{2.24} \times 0.7 \times 60$ or 375 mM of sodium bicarbonate or sodium lactate.

If the carbon dioxide content of the serum is unknown, a safe average dose of sodium bicarbonate or sodium lactate is 5.0 mM per kilo of body weight (Darrow, 1940). If this does not relieve the symptoms of acidosis, one may give a subsequent injection.

Diarrhea. The specific clinical conditions characterized by loss of extracellular fluid and a disturbance in acid-base equilibrium may now be briefly considered. The intestinal juices are isotonic with other fluids of the body. They contain the same concentration of sodium as the extracellular fluid, but the concentration of bicarbonate is higher and that of chloride lower. Therefore, diarrhea will cause not only a loss of fluid and base, but acidosis is also likely to occur. Obviously, the cause of the diarrhea should be treated, but in addition attention must be immediately focused on the restoration of body fluid. If acidosis is not pronounced, the parenteral administration of large amounts of isotonic sodium chloride solution is adequate. If desired, fluids more closely approximating the composition of interstitial fluid may be employed. A severe acidosis demands the administration of solutions containing bicarbonate or lactate.

As already mentioned, loss of extracellular fluid is accompanied by an anhydremia. This decrease in circulatory blood volume evokes compensatory vasoconstriction in order to maintain the blood pressure. Often, however, anhydremia may become so severe that an adequate circulation cannot be maintained. Tissue anoxia results and quickly causes a loss of capillary tone and an increase in permeability. Therefore shock often accompanies severe fluid loss, and shock therapy should be instituted. Shock is likely to accompany any marked extracellular fluid loss.

If diarrhea is acute, the patient experiences marked thirst. If large amounts of water are ingested, there occurs a fall in the sodium concentration of the extracellular fluid and a hydration of body cells. The administration of sodium chloride corrects this abnormal distribution of body fluids.

The volume of fluid required in cases of anhydremia depends upon the severity of the dehydration. Darrow (1940) estimates that in severe anhydremia about one-third of the extracellular electrolyte has been lost from the body. Since the extracellular fluid represents 25 per cent of the body weight, it is necessary to administer an amount of isotonic fluid equal to $\frac{1}{4} \times \frac{1}{3}$ or $\frac{1}{12}$ of the body weight.

Vomiting. The gastric juice is isotonic with the extracellular fluid reservoir of the body. It may vary greatly in composition, however, and often contains considerable base. When vomiting is persistent, large amounts of alkaline intestinal juices may find their way into the stomach and be evacuated. Consequently, persistent vomiting is always characterized by a loss of extracellular fluid containing electrolytes in isotonic concentration, but the disturbance in acid-base equilibrium may be either an alkalosis or an acidosis. If an alkalosis is present, isotonic sodium chloride solution will serve to correct both the alkalosis and the fluid loss. If, on the other hand, there is severe acidosis, the administration of sodium chloride solution should be accompanied by sodium bicarbonate or lactate.

Diabetic Acidosis. This condition is more complicated with respect to fluid and electrolyte loss than those cited in which isotonic fluid is lost from the gastrointestinal tract. The excretion of large amounts of glucose in the urine is accompanied by diuresis, and this results in a loss of fluid and sodium salts. A further loss of sodium attends the excretion of organic acids. This sodium is obtained at the expense of the bicarbonate anion. The end-result is a loss of extracellular fluid and electrolyte accompanied by anhydremia and acidosis. Treatment consists in the replacement of body fluids and the administration of glucose and insulin. The details of this procedure are discussed elsewhere (page 1225).

Nephritis. Dehydration may accompany acute and chronic nephritis and may arise from such causes as persistent vomiting or loss of sodium salts in the urine. Often this sodium loss is of significance only because the patient is on a diet restricted in salt. Symptoms of dehydration or deviations from the normal in the chemistry of the blood are indications for the administration of sodium salts either orally or parenterally, as the case may require.

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CHAPTER 33

CATIONS: POTASSIUM, CALCIUM, MAGNESIUM, BARIUM AND AMMONIUM

POTASSIUM

Potassium is the chief cation of the cells of the body. The concentration of potassium in the serum and other extracellular fluids is uniformly low throughout the animal kingdom, and in human serum it is approximately 20 mgm per cent (four to five mEq). In the cell, however, potassium salts are present in sufficiently high concentration to make the cellular fluid isotonic with extracellular fluid. No other ion can take the place of potassium in the cell, and it therefore follows that the daily intake of potassium must be as great as the excretion in order that the composition of cells be kept constant. Also growing animals must be in a positive potassium balance in order that they may form new tissue of a normal composition with respect to electrolyte. It also follows that cellular destruction will be accompanied by a negative potassium balance. Indeed, it has been shown that during starvation an animal loses potassium in proportion to nitrogen, indicating that the source of both elements is body tissue.

Absorption, Distribution and Excretion. Potassium is readily absorbed from the gastro-intestinal tract and parenteral sites of administration. The source of potassium is the diet which invariably supplies an adequate amount, inasmuch as the ion is widely distributed in all plant and animal cells. Potassium which is not retained by the organism for cell composition is rapidly excreted. The kidney tubules reject potassium efficiently and even if large amounts are given by mouth, the salts of this ion are excreted so quickly that it is difficult to detect any change in the blood concentration of potassium. This renal rejection of potassium is the basis for the *diuretic action* of potassium salts.

Pharmacological Actions. The potassium ion, although necessary to cell function and a building stone in cell structure, is a highly toxic substance when present in extracellular fluid in a concentration only one-eighth to one-tenth that found within the cell. In this extracellular site, the ion has marked effects on muscular and nervous activity and can cause death from cardiac depression. Conversely, complete potassium deprivation is not for long compatible with life. The rôle of potassium in physiological processes has been reviewed by Fenn (1940).

Potassium Deprivation. Schrader, Prickett and Salmon (1937), studying the effect of potassium deficiency, noted that rats placed on diets practically devoid of potassium but adequate in all other respects stopped growing almost immediately. In addition, the animals developed short fur-like hair, cyanosis, abdominal distention and lethargy leading to coma and death. The average survival period on the potassium deficient diet was

23 days. Pathological changes were observed in the intestine, pancreas, kidney and heart and ascites was a common finding. This work is only of academic interest for depletion of potassium is difficult even experimentally, and never occurs unless highly purified artificial diets are fed.

Cardiac Action. The potassium ion is necessary for normal cardiac function. In the absence of potassium, the isolated perfused mammalian heart will stop beating in systole. This can be corrected by adding potassium salts. On the other hand, if the concentration of potassium in the perfusion fluid is too high the heart will once again fail, but this time in diastole due to a direct depressant action of the ion on the myocardium. The action of potassium on the heart is a dual one, the ion affecting both impulse conduction and muscle contractility. Not all portions of the heart are equally sensitive to potassium, the nodal tissue being more resistant to changes in potassium concentration than is either the auricle or the ventricle. It is interesting to note that in the absence of potassium, the heart will not respond to vagal stimulation. This fact is related to the rôle of potassium in the transmission of the nerve impulse.

Winkler, Hoff and Smith (1938) have administered potassium chloride to dogs by slow intravenous infusion and have correlated changes in the electrocardiogram with serum concentration of potassium. They found that alterations in the T wave appeared at serum concentrations of five to seven mEq per liter, depression of the S-T segment at eight to 10 mEq per liter, intraventricular block at 10 mEq per liter, disappearance of P waves at nine to 11 mEq per liter, and cardiac arrest at 14 to 16 mEq per liter.

The Rôle of Potassium in the Transmission of the Nerve Impulse. Most investigators believe that potassium plays an important rôle in the transmission of the nerve impulse. The ion is apparently concerned in the functional activity of both the voluntary and autonomic nervous system. If the concentration of potassium in the fluid bathing a somatic nerve is increased, the excitability of the nerve is reduced and the amplitude of the action current diminished. By further increasing the potassium concentration it is possible to block nerve conduction. Thus the potassium ion may be said to have a local anesthetic action. Indeed, potassium potentiates the local anesthesia produced by cold. The mechanism of action of potassium in nerve conduction is not clearly understood. It is believed that the momentary outward diffusion of potassium ions from the nerve fiber which occurs when a nerve is stimulated is an essential factor in the development of the potential change accompanying the conduction of the nerve impulse.

It has been known for many years that the potassium ion is associated in some way with the transmission of the autonomic nerve impulse. In 1906, Howell observed that potassium salts produced a vagus-like inhibition of the heart and also that stimulating the vagus nerve to the perfused dog heart increased the potassium content of the perfusion fluid. Indeed, when the chemical transmission of the autonomic nerve impulse was first suggested, the potassium ion was considered the possible chemical mediator. It is now known that acetylcholine is liberated at cholinergic nerve endings and is the chemical agent which stimulates the end-organ. Linked with this process in some manner is the potassium ion. For example, if an autonomic ganglion is perfused with a fluid containing four times the normal concentration of potassium, there is a liberation of acetylcholine. If this same concentration of potassium is perfused through a denervated ganglion, the ganglion cells are stimulated without the intervention of acetylcholine. Also this ion normally appears in ganglionic perfusion fluid after preganglionic nerve stimulation.

Although these facts might appear to show that potassium is the chemical agent causing the ganglionic discharge, nevertheless the vast bulk of evidence supports acetylcholine as the true chemical mediator. The movement of potassium ions, however, is in some way concerned with the release of acetylcholine. There is no doubt, moreover, that the potassium ion itself is capable of exerting some direct stimulatory effect and it may enhance the action of acetylcholine. Evidence which minimizes the rôle of potassium in ganglionic transmission is obtained from the action of ganglionic blocking drugs. For example, curarine applied to a ganglion will prevent the stimulating action of acetylcholine but not that of potassium. Inasmuch as curarine blocks normal ganglionic transmission, it is concluded that acetylcholine and not potassium is the physiological mediator of preganglionic nerve impulses.

The response of an effector organ to cholinergic nerve impulses is also associated with a release of potassium. In this case its presence would appear to be merely incidental to the response of the end-organ. For example, even after atropinization, stimulation of a cholinergic nerve leads to normal acetylcholine production but the effector organ fails to respond. Under such circumstances, potassium does not appear.

Potassium and Sympatho-Adrenal Discharge. Potassium has also been implicated as the substance responsible for the pharmacodynamic actions of epinephrine. It has long been known (Mathison, 1911) that the intravenous administration of potassium will cause a marked rise in blood pressure. Likewise the action of epinephrine is associated with a rise in the concentration of serum potassium. Camp and Higgins (1936) extended these observations in the intact animal and showed that in many ways the actions of potassium and epinephrine were similar. They concluded that all the actions of epinephrine could be attributed to the liberation of potassium. In a convincing rebuttal of this theory, Knoefel and Alles (1938) pointed out that potassium is irritating to blood vessels and that reflexes thus initiated when its salts are injected intravenously may be partially responsible for the sympathomimetic effect of potassium. More significant is the fact mentioned above and emphasized by Knoefel and Alles, namely, that potassium is capable of stimulating sympathetic ganglia, in which category the adrenal medulla must also be placed. This would result in a discharge of epinephrine and a release of adrenine by adrenergic nerves. Lastly, these authors made the pertinent observation that the actions of potassium and epinephrine on isolated organs were for the most part antagonistic.

Potassium and Muscular Dystrophies. The potassium ion markedly influences the function of skeletal muscle. Many of the effects of potassium on muscle may be secondary to the actions of the ion on nerve fibers or the myoneural junction. Familial periodic paralysis is markedly benefited by potassium therapy. Likewise the symptoms of myasthenia gravis are somewhat relieved by the administration of large amounts of potassium salts (Laurent and Walther, 1935). Potassium also has an anti-curare action, being able partially to overcome the transmission block produced by this drug at the myoneural junction (Wilson and Wright, 1936). As a physiological counterpart, it has been shown that the administration of potassium salts intensifies the symptoms of myotonia congenita (Russell and Stedman, 1936). The exact mechanism of these effects of potassium cannot be stated.

Toxicity. Potassium ions are toxic when injected intravenously in high concentration. Winkler, Hoff and Smith (1938) showed that when the potassium in the serum reaches a concentration four times as great as is normally present (15 to 20 mEq) death results from cardiac failure. In order to attain this level, however, one has to inject fairly strong solutions. There is no danger in the intravenous administration of potassium in concentrations normally characteristic of extracellular fluid. Potassium may be taken orally in large amounts without untoward effect. The ion is so rapidly excreted that very little change in its serum concentration can be detected. When kidney function is markedly impaired, however, potassium may occasionally accumulate in the body and cause toxic actions.

Adrenal Insufficiency. In Addison's disease there is a marked disturbance in the metabolism of potassium. Apparently, the renal excretion of this cation is impaired because high concentrations accumulate in the extracellular fluids (Figures 117 and 119). Some believe that many symptoms of adrenal insufficiency can be directly attributed to the retention of potassium, and assign to the hormones of the adrenal cortex a major rôle in the regulation of the metabolism of potassium. In adrenalectomized animals and in patients with Addison's disease, the oral administration of potassium salts may lead to a marked exacerbation of symptoms. Conversely, the restriction of potassium in the diet results in a considerable amelioration of symptoms. Although the exact rôle played by potassium in the syndrome of adrenal cortical insufficiency has yet to be elucidated, there is sufficient evidence to implicate this ion and to require caution in the administration of potassium salts to patients with abnormal adrenal function (page 1232). It is also of interest in connection with the influence of the adrenal cortex on potassium metabolism and the rôle of the potassium ion in neuromuscular physiology that Kuhlmann and associates (1939) have produced in dogs a diminution in the concentration of extracellular potassium by the injection of large amounts of desoxycorticosterone. As a result the animals manifested symptoms of muscular weakness which could be likened to those of familial periodic paralysis. The symptoms were relieved by the administration of potassium.

Preparations. Most of the salts of potassium are used in therapy for the action of the anion rather than the potassium cation. Included in this category are such compounds as potassium bicarbonate, potassium bromide, potassium chlorate, potassium iodide, potassium permanganate, potassium thiosulfate, etc. When the action of the cation is desired, the two salts of potassium which are most widely employed are potassium chloride and nitrate. *Potassium Chloride,* N.F., consists of colorless crystals which are very soluble in water. *Potassium Nitrate,* U.S.P., B.P., consists of a white crystalline powder having a cool saline taste. It is freely soluble in water.

Therapeutic Uses. Potassium is valuable chiefly as a *diuretic.* Its use for this purpose is discussed elsewhere (page 630). Potassium salts have been employed orally in the treatment of *paroxysmal tachycardia* and *premature systoles.* It is highly doubtful however, whether the oral route of administration can possibly be effective in raising the level of potassium in the circulation sufficiently high to have therapeutic value.

A specific therapeutic use of the potassium ion is in the treatment of *familial periodic paralysis,* a rare myopathy characterized by recurrent attacks of flaccid paralysis affecting mainly the muscles of the trunk and limbs. Associated with the periodic attacks, there is a reduction in concentration of potassium in the extracellular fluids (Pudenz and coworkers, 1938). The symptoms of a patient in an acute episode of this disease can be rapidly relieved by the intravenous or oral administration of potassium chloride. The intravenous injection of this ion is dangerous and should be reserved for emergency use only. If employed, one gram of potassium chloride in 50 cc of solution is slowly injected. The oral dose is from five to 10 grams. Remission of symptoms occurs within 30 minutes to two hours after oral administration. As a prophylactic measure, the administration of five grams of potassium chloride nightly will prevent the occurrence of attacks.

It is interesting to note, in connection with the rôle of potassium and of acetylcholine in the transmission of the nerve impulse, that Pudenz and coworkers obtained symptomatic relief of periodic paralysis by the parasympathomimetic drugs having a nicotinic action. However, this relief was also associated with a rise in the concentration of serum potassium. In connection with the relation of the adrenal cortical hormone to the metabolism of the potassium ion, it is pertinent to observe that Pudenz and coworkers could initiate attacks of familial paralysis by the injection of an active cortical extract. They believe that periodic familial paralysis results from some inborn error in metabolism which is ultimately reflected in an abnormal distribution of potassium. They present evidence suggesting that the symptoms result from a disturbance in function of the central nervous system rather than of muscle.

Potassium salts have been rather widely employed in the treatment of *Ménière's disease*. The rationale for therapy is based upon the belief that in this condition attacks are precipitated by a retention of water and electrolytes (sodium salts) and that by means of a low sodium, high potassium intake they may be prevented. Although many investigators have failed to observe any significant change in the electrolyte composition of the blood of patients suffering from Ménière's disease, most are in agreement that the symptoms are reduced in intensity in a significant number of patients receiving potassium salts. The usual dose is six to 10 grams of potassium chloride daily in divided doses. The problem of the treatment of Ménière's disease and the rôle of potassium in the syndrome have been reviewed by Talbott and Brown (1940), Walsh and Adson (1940), and Talbott and Schwab (1940).

Considerable attention has been directed to the use of potassium salts in the treatment of *diseases of allergy*. Two explanations have been offered to account for their alleged value: first, the unwarranted assumption that allergic manifestations have their basis in a disturbance in water and electrolyte metabolism, for which there is little evidence; secondly, the nebulous relationship between potassium and epinephrine. Extravagant claims have been made for the relief afforded to patients by the administration of a daily dose of potassium chloride (one gram) which represents but a fraction of the normal daily dietary intake of this widely distributed cation. Controlled studies fail to reveal any value of potassium in the relief of symptoms of diseases of allergy (Harsh and Donovan, 1940; Rubin and coworkers, 1940; Miller and Piness, 1940).

CALCIUM

Calcium is present in the extracellular fluid where it serves a variety of functions. The cation is indispensable for the maintenance of the functional integrity of the voluntary and autonomic nervous systems. It also is necessary for normal cardiac function, and is one of the factors operating in the clotting of blood. Lastly, calcium salts form the structural basis of the bony skeleton. Many pathological conditions are caused by abnormalities in calcium metabolism, especially calcium deficiency. Calcium preparations, therefore, have many therapeutic uses.

Calcium Requirements. The body is in constant need of the calcium ion. This is obtained from the diet and it is only in abnormal circumstances that this source need be supplemented. The average adult requires 0.45 gram of calcium daily, but growing children and pregnant and lactating women should ingest twice this amount.

Absorption and Excretion. Calcium is absorbed in the upper part of the intestinal tract. It is excreted in the urine and feces. Some believe that the calcium in the feces represents that part of the ingested calcium which has never been absorbed from the intestinal tract, and that all of the absorbed calcium destined for excretion finds its way into the urine. On the other hand, there is evidence that absorbed calcium may be excreted into the bowel. For example, the parenteral administration of calcium increases the amount of this ion in the feces, although McCance and Widdowson (1939) claim that after intravenous administration all of the injected calcium can ultimately be found in the urine. It has also been observed that animals on calcium-free diets will partially excrete into the intestinal tract the calcium which they liberate from their skeletal stores. However, only a portion of orally ingested calcium enters the circulation and a large part of the calcium in the feces is that which has escaped absorption. A normal individual with an adequate calcium intake excretes about 25 to 35 per cent of the ingested calcium in the urine and the remainder in the feces.

There are certain factors which influence the absorption and excretion of calcium. Many calcium salts are insoluble and the absorption of calcium from the intestine is promoted by factors which keep calcium in solution. An acid reaction in the intestine promotes calcium absorption by favoring solution of the calcium salts, whereas an alkaline reaction precipitates calcium and decreases absorption. Therefore, calcium is absorbed mainly in the upper intestinal tract. The administration of hydrochloric acid increases calcium absorption whereas alkalis affect absorption adversely. The presence of large amounts of unabsorbed fatty acids in the intestinal tract also interferes with absorption because insoluble calcium soaps are formed. The absorption of calcium is also decreased by diarrhea. Lastly, an adequate intake of vitamin D is necessary for normal calcium absorption.

The State of Calcium in the Blood and Its Distribution in the Body. The greatest amount of calcium in the body is present in the skeleton. Normal dry marrow-free bone contains by weight 60 per cent calcium in combination with phosphate and carbonate. This calcium usually remains fixed, but under conditions of inadequate calcium intake, increased calcium requirements or abnormal calcium metabolism, the bones give up calcium to the blood. The remainder of the body calcium is in the extracellular fluid, there being no calcium in the cells. Serum normally contains 9.0 to 11.5 mgm per cent (five mEq per liter) of calcium.

Calcium is present in serum in a higher concentration than can be dissolved in an aqueous solution containing as much phosphate and carbonate as the serum. It is believed that the serum calcium can be divided into three fractions: (1) A small part estimated as ranging from 1.2 to 2.5 mgm per cent is in true solution. (2) A portion is held in solution by the serum proteins, the amount being directly proportional to the concentration of protein. In an individual with seven grams per cent of serum protein, approximately 3.9 mgm per cent of calcium will be in solution by virtue of its loose combination with protein. (3) The large portion of calcium which remains unaccounted for probably exists as a supersaturated solution of calcium phosphate and calcium carbonate, or as soluble calcium complexes. It is this latter portion of the dissolved calcium which is thought to be under the influence of the parathyroid gland.

The concentration of serum phosphate and serum protein can alter the level of serum calcium. Large amounts of phosphate precipitate calcium salts out of solution, whereas a low phosphate concentration allows for greater calcium solubility. Also, any change in the concentration of serum protein will affect the amount of calcium held in solution by protein.

Ionized and Non-ionized Calcium. Only the calcium in ionic form is physiologically active. That fraction of the serum calcium which is in combination with protein is non-ionized, and can be materially reduced without producing any of the symptoms associated with hypocalcemia. It is necessary to know the protein as well as the calcium level of the serum in order properly to interpret the physiological significance of the calcium level of the blood. Ionized calcium is free to diffuse into the other extracellular fluids. However, it follows that the concentration of calcium in the interstitial fluid is lower than in the serum, inasmuch as calcium bound to protein cannot transverse the capillary wall. Thus, the cerebrospinal fluid normally contains only about five mgm per cent of calcium compared with 10 mgm per cent for serum.

Pharmacological Actions

Local Action. Certain salts of calcium, notably the chloride, are intensely irritating to tissue. Calcium chloride, although not irritant to the intact skin, will cause painful sloughing if injected subcutaneously. Thus, when calcium chloride is administered parenterally it must always be given by vein and great care should be exercised so that none of the solution extravasates into the surrounding tissue.

Nervous System. An excess of calcium has little effect on the function of the nervous system, but a reduction in the ionized calcium leads to a serious physiological disturbance, known as *low-calcium tetany,* characterized by an increased irritability of all types of muscle. The symptoms most often observed are carpopedal spasm, laryngospasm and convulsions. An increased activity of smooth muscle is evidenced by spasm of the ciliary muscle, sphincter of the iris, esophagus, gastro-intestinal tract, bladder and bronchi. Cardiac muscle likewise is affected and arrhythmias occur.

Site of Action of Calcium on the Nervous System. Calcium deficiency primarily affects the peripheral neuromuscular mechanism. For example, if the peripheral end of the cut motor nerve of a calcium deficient animal is stimulated, it can be demonstrated that the muscle is still excessively responsive. Also, if an isolated limb is perfused with a calcium-free fluid, fibrillary twitchings and spasms of the muscles are soon observed. That the muscle itself is not hyperirritable can be shown in curarized animals. When the effects of the nerve impulse are blocked by curare, no abnormal muscle activity is noted. This is also true if the peripheral motor nerve is cut and degenerated.

There is a definite distinction between the localized fibrillary twitchings and the clonic and tonic convulsions which occur in low-calcium tetany. It was once believed that the gross muscular contractions resulted from stimuli arising in the midbrain for it had been reported that this type of response could not be observed in spinal animals. West (1935), however, concluded that the neuromuscular disturbance was peripheral and that only the integrity of the spinal reflex arc was needed for the characteristic tonic and clonic tetany to occur. Thus, a high transection of the spinal cord failed to prevent either fibrillary twitchings or the convulsive type of movements. On the other hand, interruption of the reflex arc on the afferent side by dorsal root section eliminated all but the fibrillary muscular twitchings.

The actions of calcium on the nervous system have been studied in detail by Bronk and his associates. They have found that autonomic ganglion cells are stimulated by a decrease in calcium concentration so that the cells are more readily discharged by acetylcholine, may show repetitive after-discharge following a preganglionic volley or may discharge spontaneously. High concentrations of calcium block synaptic transmission (Bronk and coworkers, 1938; Bronk, 1939). Also the threshold of nerve fibers for electrical stimulation is reduced (Brink and coworkers, 1939).

Etiology of Low-Calcium Tetany. Hypocalcemia with its resulting tetany can arise from a variety of causes and it is often difficult to ascertain the basic defect in the calcium metabolism. The more important conditions characterized by hypocalcemia are the following:

(1) *Calcium and vitamin D deprivation* is a common cause of tetany during infancy, and during pregnancy and lactation. The level of blood calcium is invariably low, that of phosphorus low or normal. Pathological changes in the bones usually accompany a long-standing calcium and vitamin D deficiency. In infants, rickets results; in adults, osteomalacia.

(2) *Parathyroprivic tetany* may be idiopathic or postoperative in origin. The hypocalcemia is accompanied by and indeed may be the result of an abnormally high concentration of serum phosphate.

(3) *Failure to absorb sufficient calcium* despite an adequate dietary intake may result in hypocalcemia and associated tetany. *Celiac disease, sprue,* and *steatorrhea* are conditions often complicated by a calcium deficiency. Both the calcium and phosphorus concentrations of the blood are reduced. There may be an associated osteoporosis.

(4) *Certain chemical agents* can either precipitate calcium or form non-ionized chemical complexes and thus cause hypocalcemic tetany. The most important of these are the citrates, oxalates and phosphates. The feeding of large amounts of phosphate will readily convert a latent tetany to a manifest form.

(5) *A rise in the pH of the blood* can cause tetany, believed to be of low-calcium origin. Although the concentration of total calcium is little affected, an increase in alkalintiy will reduce the amount of ionized calcium. Hyperventilation and prolonged vomiting may both give rise to an alkalosis and tetany. The administration of large amounts of bicarbonate may also have the same effect. The tetany which follows vomiting is known as *gastric tetany*.

It must be remembered that neuromuscular disturbances simulating those associated with hypocalcemia characterize certain diseases and drug intoxications. These include meningitis and uremia, and guanidine, strychnine, lead, etc.

Circulatory System. *Heart.* Either a deficiency or an excess of the calcium ion alters the function of cardiac muscle. In early experiments on the perfused heart, it was learned that an antagonism exists between the effects of calcium and potassium on the heart. In the absence of calcium, the characteristic action of potassium becomes prominent and the heart stops beating in diastole. On the other hand, an excess of calcium causes systolic arrest, so-called "calcium rigor."

No such circumspect results, however, occur when calcium is injected into intact animals. Hoff, Smith and Winkler (1939) have studied the electrocardiographic changes in dogs perfused with calcium at such a rate that the blood concentration of this ion slowly rose from normal to toxic levels. A bradycardia, probably of vagal origin, and T wave changes occurred when the blood calcium averaged 29 mgm per cent. Death occurred either from ventricular fibrillation at an average calcium level of 60 mgm per cent, or from cardiac slowing with gradual arrest at higher calcium levels. The above investigators suggested that calcium in low concentrations is a direct cardiac stimulant, in high concentrations, a direct muscular depressant, and that the balance between the depressant and irritant actions determines the type of cardiac death.

The cardiac action of calcium in some ways resembles that of digitalis. High concentrations of calcium in the circulation have been reported to increase the toxicity of digitalis.

Capillary Permeability. Calcium is said to decrease the permeability of the capillaries. There is little experimental evidence in support of this contention. Calcium is also thought to affect the permeability of all tissue cells but the evidence is based mainly upon studies of unicellular organisms. Nevertheless, calcium salts are widely used therapeutically for the prevention of effusions and for the control of inflammation and edema, as in angioneurotic edema, urticaria, asthma, pleurisy, etc. It is generally believed that the results obtained are not worth the trouble of calcium administration. Tainter and Van Deventer (1930) could demonstrate no anti-edemic action of calcium in experimental edemas.

Blood Clotting. Calcium is necessary for the normal clotting of blood. It is involved in the conversion of prothrombin to thrombin. It is doubtful whether a calcium deficiency is ever responsible for prolonged bleeding time, as encountered clinically, and the administration of calcium salts has no significant effect in reducing the clotting time.

Uterine Muscle. The uterus, like the heart, is dependent upon an optimal concentration of calcium ions for normal muscular activity. This has been convincingly demonstrated by Danforth and Ivy (1939) who showed in post partum experimental animals that uterine activity was depressed when the concentration of ionized calcium in the blood was diminished. What is more the organ became insensitive to oxytocic drugs. Also the effects of oxytocic drugs could be potentiated by the calcium ion. Danforth and Ivy suggest that those rare instances in which the post partum uterus is insensitive to oxytocics may be due to a relative deficiency of ionized calcium. They also point out the possibility that the administration of alkalinizing salts to reduce the concentration of ionized calcium might be of therapeutic value in diminishing excessive irritability of the uterus in cases of threatened abortion or in relieving uterine tetany.

Diuretic Action. Calcium chloride is an acid-forming diuretic salt. The mechanism of acid formation and diuresis are discussed elsewhere (page 630).

Antacid Action. The basic salts of calcium, particularly the carbonate, are employed as antacids in the control of gastric acidity (page 786).

Antispasmodic Action. There are clinical reports suggesting that the calcium ion exerts a definite antispasmodic action on smooth muscle. The intravenous injection of calcium salts has apparently proved beneficial in the control of intestinal, renal and gall bladder colic (Bauer, Salter and Aub, 1931). However, there is little experimental evidence in support of this use of calcium. For example, Fitzhugh, Miller, Taylor and Aub (1931) observed no effect of calcium on the hyperperistalsis resulting from intestinal obstruction or administration of eserine in dogs.

Preparations and Routes of Administration. There are several important preparations available when the systemic action of calcium is desired. These differ in their calcium content and their permissible routes of administration.

Calcium Chloride ($CaCl_2 \cdot 2H_2O$), U.S.P., contains 27 per cent calcium, and consists of white granules freely soluble in water. The B.P. preparation is anhydrous and therefore contains a higher percentage of calcium. The chloride salt of calcium is especially valuable in the treatment of calcium tetany. In addition to its high content of available calcium, it is an acid-forming salt, and by reducing the pH of the blood it further increases the concentration of ionized calcium. The salt can be given either by mouth or intravenously. *It must never be injected into tissues.* It is somewhat irritating to the gastro-intestinal tract and should be administered in some demulcent vehicle, such as milk. Calcium chloride is also irritating to veins. Injections are accompanied by peripheral vasodilatation and a subjective cutaneous burning sensation. For intravenous administration, the salt is usually given in a concentration of five to 10 per cent. Injection rate should be slow (not over one to two cc per minute) to prevent a high concentration of calcium from reaching the heart. Otherwise, there is a real danger of cardiac syncope. A moderate fall in blood pressure due to vasodilatation may attend the injection.

Calcium Gluconate ($[CH_2OH(CHOH)_4 \cdot COO]_2Ca \cdot H_2O$), U.S.P., contains nine per cent calcium, and is a white crystalline or granular powder, odorless, tasteless and soluble 1:5 in boiling water. It can be administered orally, intravenously or intramuscularly. Although much lower in calcium content than the chloride, it has the marked advantage that it is non-irritating either to the tissues or the gastro-intestinal tract. For intravenous injection, calcium gluconate is administered slowly in a 10 per cent solution, which strength is also used for intramuscular injection.

Calcium Lactate ($Ca[C_3H_5O_3]_2 \cdot 5H_2O$), U.S.P., B.P., contains 13 per cent calcium. Its physical properties are similar to those of the gluconate. It is given by the oral route. In treatment of tetany, its action is apparently enhanced by the simultaneous administration of lactose.

Precipitated Calcium Carbonate, U.S.P., (*Calcium Carbonate,* B.P.), is an insoluble fine, white, microcrystalline powder containing 40 per cent calcium. It can only be used orally. After ingestion, it is converted to soluble calcium salts in the bowel and calcium is made available for absorption.

Tribasic Calcium Phosphate, U.S.P., although chiefly used as a gastric antacid, is a valuable source of the calcium ion, especially when it is desired to supply both calcium and phosphorus. It is an insoluble, tasteless white powder that must be given orally. *Calcium Phosphate,* B.P., is a mixture of basic and acid salts.

Other calcium preparations are described in connection with the gastric antacids (page 786).

Therapeutic Uses. Calcium salts are specific in the treatment of *low-calcium tetany* irrespective of etiology. Even the tetany associated with parathyroid deficiency can largely be controlled by calcium rather than hormonal therapy. In severe manifest tetany, the symptoms are best brought under control by intravenous medication. Five to 20 cc either of five per cent calcium chloride or 10 per cent calcium gluconate are injected slowly. For the control of milder symptoms or latent tetany, oral medication suffices. Average doses are *calcium chloride,* six to eight grams daily in divided doses, best given in milk; *calcium gluconate,* 15 grams daily in divided doses; *calcium lactate,* four grams, plus lactose eight grams, with each meal; *calcium carbonate* or *calcium phosphate,* one to two grams with meals, as a watery suspension or sprinkled on food. With preparations other than the chloride, an *acidifying agent* such as ammonium chloride or hydrochloric acid is helpful by increasing the proportion of ionized calcium in the blood. Hydrochloric acid will also increase calcium absorption. *Vitamin D* or *parathyroid extract* may also be given when warranted by the etiology of the tetany.

Mention has been made of the *antispasmodic action* of calcium. Successful results have been reported in the treatment of intestinal, ureteral and gall bladder colic. Calcium salts are also effective in relieving the abdominal pain, diarrhea and tenesmus of intestinal tuberculosis. The slow intravenous injection of 10 to 20 cc of five per cent calcium chloride solution is the procedure most often employed for eliciting an antispasmodic action, although calcium gluconate is safer and easier to administer.

The *anti-edemic action* of the calcium ion has been discussed. The use of calcium chloride as a *diuretic* is discussed on page 631, and the use of calcium as an *antacid* is presented on page 789.

MAGNESIUM

Magnesium, like calcium, is an ion of considerable physiological importance and pharmacological interest. Magnesium is indispenable to life in the mammalian organism. Apparently, it is essential for the functional integrity of the neuromuscular system. In high concentrations, it is a central nervous system depressant. There is also evidence that magnesium is necessary for the activation of animal phosphatases and is an important substance in the dephosphorylation process in muscle. Magnesium is also an essential constituent of the plant world. It is present in the chlorophyl molecule and is believed to be vital for the function of this pigment.

Absorption, Distribution and Excretion. Magnesium is absorbed with difficulty from the gastro-intestinal tract. Factors influencing magnesium absorption are the same as those affecting calcium inasmuch as the salts of both these ions have similar physical properties. Absorption is enhanced by an acid reaction in the duodenum, and retarded by an alkaline reaction. In the serum, magnesium is normally present in a concentration of two to three mgm per cent. About 80 per cent of the serum magnesium is ionized and diffusible. The remainder is probably bound to protein. Unlike calcium, the concentration of magnesium in erythrocytes is higher than in the serum, being four mgm per cent. Magnesium is present in the cells of other tissues in a concentration higher than calcium and is present in muscle cells in unusually high amounts (about 21 mgm per cent).

Magnesium is excreted mainly in the urine, although a small amount may be eliminated into the intestinal tract. The kidney excretes magnesium so rapidly that the oral ingestion of magnesium salts results in only a slight rise in the serum magnesium. The ingestion of magnesium not only increases the total excretion of calcium but also increases the urinary fraction of excreted calcium.

Local Actions. The basic magnesium salts are effective *antacids* and are employed to neutralize gastric secretion. The compound usually prescribed for this purpose is magnesium oxide. Magnesium is slowly absorbed from the intestinal tract and magnesium salts thus hold water in the bowel. This results in a *cathartic action*. The salts commonly used for this purpose are magnesium sulfate (Epsom salt) and magnesium citrate.

Magnesium sulfate applied locally to nerve acts as an anesthetic. This *local anesthetic action* is not preceded by stimulation and is a specific effect of the magnesium ion. Very high concentrations are needed to produce this action which is therefore of little practical value. However, it does allow hypertonic magnesium salts to be injected for other purposes with a minimum of pain.

Magnesium salts applied to isolated intestinal strips in low concentration exert an *antispasmodic action,* decreasing both tone and peristaltic activity and antagonizing the stimulation produced by physostigmine and barium. No clinical use can be made of this action of magnesium because the dose required is too great. When magnesium salts are used as a cathartic, intestinal depression is readily overcome by the mechanical stimulus of the fluid which the magnesium retains in the bowel.

When hypertonic solutions of magnesium sulfate are introduced into the duodenum, there is a temporary increase in the *flow of bile*. This is probably the result of the relaxation of the sphincter of Oddi and a subsequent emptying of the gall bladder, rather than the result of increased secretion of bile.

Magnesium Deprivation. Magnesium deprivation has been extensively studied by Kruse, Orent and McCollum (1933, *et seq.*) who fed dogs and rats a diet containing only 1.8 parts of magnesium per million. Symptoms obtained in both species were vasodilatation, hyperirritability, cardiac arrhythmia, spasticity, and tonic and clonic convulsions. Death followed unless the ion was supplied.

Similar observations have been made by Greenberg and associates (1938). Hirschfelder and Haury (1934) have reported human cases of parathyroid tetany associated with very low concentrations of plasma magnesium which were relieved by the oral administration of magnesium salts.

Systemic Actions. *Magnesium Depression.* Parenteral administration of large amounts of magnesium salts results in marked depression. Both the central nervous system and the peripheral neuromuscular apparatus are affected. Peripherally, magnesium has a curare-like action. The excitation of voluntary muscle by nerve impulses is prevented. Magnesium blocks muscular contraction produced either by electrical stimulation of motor nerves or by drugs such as acetylcholine and physostigmine. The mechanism of this action is unknown.

Magnesium also produces a true depression of the central nervous system. For a time, it was argued that this depression was entirely referable to the peripheral muscular paralysis. It has been shown, however, that animals are rendered unconscious before the muscles lose their ability to respond to stimulation. A high concentration of magnesium in the serum is necessary to produce this central response. In the dog, Neuwirth and Wallace (1929) found that a mild depression is produced if the level of serum magnesium exceeds five mgm per cent and that complete anesthesia attends a blood level of 20 mgm per cent. All portions of the central nervous system are apparently affected for there is a loss of all reflexes, a continuous fall in blood pressure and a paralysis of respiration. It is the vulnerability of vital medullary centers to magnesium which renders its clinical use as a central depressant so dangerous.

Calcium Antagonism of Magnesium Depression. The central depression produced by the magnesium ion can be completely antagonized by calcium. An animal anesthetized by magnesium will return to consciousness and behave normally a few seconds after the intravenous administration of sufficient calcium. There is no acceptable explanation either for magnesium narcosis or calcium antagonism. It is interesting, however, that whereas a low concentration of either of these ions in the blood leads to similar functional changes both in the central nervous system and the peripheral neuromuscular apparatus, an excess of calcium will antagonize and not synergize the effects of an excess of magnesium.

Action on Heart Muscle. The magnesium ion is depressant to heart muscle. High concentrations resulting from parenteral administration cause bradycardia, conduction disturbances and eventually cardiac arrest (Smith, Winkler and Hoff, 1939). It is usually the respiration, however, which fails before the circulation after systemic administration of magnesium.

Magnesium Poisoning. Magnesium poisoning rarely occurs, for after the oral ingestion of magnesium salts the normal kidney is capable of excreting the ion with sufficient rapidity to prevent the accumulation of toxic amounts. In the event of impaired renal function, however, the oral administration of magnesium salts may sometimes lead to poisoning despite the slow rate of absorption of magnesium salts. This is likely to occur when magnesium sulfate is employed as a dehydrating cathartic in the treatment of the edema of nephritis. The ensuing symptoms of central depression may be mistaken for uremia. The blood pressure falls and death results from respiratory paralysis. Artificial respiration should be administered until calcium salts can be injected intravenously to antagonize magnesium.

Preparations. Magnesium citrate and sulfate are the salts usually employed for their action on the gastro-intestinal tract (page 806). Magnesium oxide and carbonate are preparations of choice as antacids (page 785). Magnesium trisilicate is used as an antacid and adsorbent (page 785). For parenteral administration, magnesium sulfate is always used.

Therapeutic Uses. Magnesium has been used extensively in therapeutics but the validity of many of the applications of this ion can be seriously questioned.

Gastro-intestinal Uses. The uses of magnesium salts as *cathartics* and *antacids* are discussed elsewhere (pages 805, 790). Magnesium sulfate has been employed as a *cholagogue,* especially in chronic cholecystitis and catarrhal jaundice. Hypertonic magnesium sulfate in the intestine increases the flow of bile into the duodenum, probably merely by relaxing the sphincter of the common bile duct.

Use as a Central Depressant. Magnesium sulfate has been used as a central depressant, especially in *convulsive syndromes.* The dose for children is 0.1 to 0.2 cc per kg of a 25 per cent solution, given intramuscularly. In *eclampsia,* the usual dose is 10 cc of a 25 per cent solution given intramuscularly, and repeated in five cc amounts every half hour until relief is obtained. (For the Stroganoff technic, *see* Stroganoff and Davidovitch, 1937.) The symptoms of *tetanus* can be relieved by parenteral administration of magnesium sulfate. The subcutaneous or intramuscular injection of two cc of a 25 per cent solution per 20 pounds of body weight may afford relief for several hours. For immediate effects, magnesium sulfate may be injected intravenously, if great care is exercised, in six per cent solution at a rate not exceeding three cc per minute until relaxation is obtained. After intravenous administration, magnesium sulfate is effective only for approximately 30 minutes. For long-sustained action, magnesium sulfate may be injected intrathecally. The usual dose employed is one cc of a 25 per cent solution for every 20 pounds of body weight. The muscular relaxation obtained lasts 12 to 30 hours. The barbiturates have largely replaced magnesium sulfate as the agents of choice in the control of convulsive syndromes.

Magnesium is capable of augmenting the action of general anesthetics and morphine, and has been employed in *obstetrical anesthesia.* Gwathmey introduced a routine technic in which the rectal administration of ether in oil is combined with the intramuscular injection of magnesium sulfate and morphine sulfate. The magnesium salt is given at intervals in doses of two cc of a 50 per cent solution. For details, the interested reader is referred to the report of Harrar (1927).

When using magnesium sulfate as a central and neuromuscular depressant, one must constantly guard against respiratory failure. Should this failure occur, it can best be combated not by respiratory stimulants but rather by intravenous calcium, for this latter ion successfully counteracts the depressant actions of magnesium. A solution of calcium gluconate or chloride for intravenous administration should always be available.

Magnesium sulfate is used for the local treatment of *erysipelas.* A cold wet compress of saturated magnesium sulfate solution in water or in 50 per cent glycerin is applied directly to the afflicted skin area and affords considerable symptomatic relief. The action has been dually ascribed to the osmotic effect of this salt in drawing water from the lesion and to a local anesthetic action on peripheral sensory nerves.

BARIUM

Barium is an extremely toxic element when absorbed. The insoluble barium sulfate is widely employed in medicine as an *opaque contrast medium for roentgenographic purposes* and as an *antidiarrheal and demulcent powder.* The only application of the systemic action of barium is in the use of the soluble barium chloride for the treatment of complete heart block.

Systemic Actions and Toxicology. The characteristic systemic action of barium is a marked stimulation of muscles of all types, regardless of innervation. In poisoning by soluble barium salts, the major signs and symptoms are related to this powerful muscular stimulation. The action of barium on the gastrointestinal musculature causes vomiting, severe colic and diarrhea, and hemorrhage. The cardiovascular effects consist of a marked hypertension due to spasm of the arteriolar musculature, intense myocardial stimulation, and ultimately death from cardiac arrest. In addition, there are convulsive tremors of skeletal muscles. Paralysis of the central nervous system may develop late in the course of barium intoxication. The fatal dose of a soluble barium salt is about 0.8 gram. Death usually occurs within an hour, but may be delayed for some time.

Poisoning may occur in industry or from the accidental use of a soluble barium salt in x-ray work. Even barium carbonate or sulfide is sufficiently soluble in the intestinal fluids to be absorbed in toxic amounts.

Treatment of barium poisoning consists in the precipitation of the unabsorbed salt remaining in the intestinal tract by the ingestion of a solution of sodium or magnesium sulfate, which forms the insoluble barium sulfate and also acts as a cathartic to hasten the passage of the barium out of the bowel. Therapy is otherwise purely symptomatic and supportive. The cautious intravenous use of calcium or magnesium salts may be tried in an attempt to antagonize the muscular action of barium. Cardiac pain should be relieved by morphine if necessary.

Cardiac Action. The only systemic use of barium is for its action on the heart in certain selected cases of complete heart block. The cardiac effects of barium were known for many years but the drug was considered too toxic to be used clinically. Barium has a digitalis-like action on the heart muscle, but lacks a specific effect on the conduction system. Both the force of contraction and the excitability of the myocardium are increased. The rate is especially accelerated if it has been abnormally slow. The increase in rate is the basis for the use of barium in Stokes-Adams disease.

Clinical Use of Cardiac Action. In complete auriculoventricular dissociation, the idioventricular rate is usually between 20 and 40 beats per minute. When the rate drops too low, or when periods of ventricular asystole lasting several seconds occur, fainting spells and convulsive seizures may ensue due to cerebral anemia. If syncopal seizures develop, the disease is known as Stokes-Adams syndrome and may require therapy. Therapy is designed to increase the ventricular rate. The drugs of choice are epinephrine and ephedrine. In some patients, however, barium gives dramatic relief.

Barium chloride was introduced for the symptomatic therapy of Stokes-Adams disease in 1925 by Cohn and Levine. The degree of heart block is not altered, but the syncopal spells may be alleviated. Even when the heart rate is not increased by barium, the periods of marked bradycardia and asystole are prevented. Whether the barium acts on the idioventricular pacemaker or creates some ectopic focus in the ventricle for initiating impulses is unknown.

Barium chloride is used in doses of 30 mgm, given three or four times daily. It is taken orally, well diluted. If necessary, the dose may be cautiously increased to 40 or 50 mgm, four times daily. When the syncopal attacks are controlled, the drug is discontinued. This usually occurs within from a few hours to a day or two.

Results with barium are not uniformly good, and some authors have reported failure. The drug is worth trying, however, when other measures are ineffective. Cohn and Levine (1925) reported one case which became steadily worse despite the use of epinephrine, atropine and digitalis. By the time barium was decided upon, the patient was in a convulsive state and was conscious only half the time. The day after barium therapy was initiated, the patient was entirely free of attacks and remained so for weeks without further treatment. If the syncope is due to periods of ventricular prefibrillation rather than to periods of asystole or excessive bradycardia, barium is perhaps less likely to precipitate fatal ventricular fibrillation than is epinephrine or ephedrine.

Other Uses of Barium. The local uses of insoluble barium salts are discussed elsewhere.

Preparations. *Barium Sulfate,* U.S.P., B.P., is a fine, white, odorless, tasteless, and bulky powder, free from grittiness. It is insoluble in water. In prescribing *barium sulfate,* the title should always be written out in full to avoid confusion with the poisonous barium sulfide or sulfite. *Barium chloride* is quite soluble in water. Great care must be observed in prescribing this drug and the upper limits of allowable dosage should never be exceeded.

AMMONIUM COMPOUNDS

The ammonium ion (NH_4^+) plays an important rôle in the body, being intimately concerned with the regulation of the acid-base equilibrium. It can be formed from urea by the renal cells and in conditions of acidosis it is combined with anion and thus spares the fixed base of the body fluids. The resulting ammonium salt is eliminated in the urine. The urea formed in the metabolic processes of the organism serves as a source of the ammonium ion.

Pharmacological Actions. *Central Nervous System.* Neutral ammonium salts have a toxic action on the central nervous system. The ammonium ion stimulates the cord and the vasomotor and respiratory centers of the medulla. Toxic concentrations cause tonic convulsions. This stimulant action of the ammonium ion has no therapeutic application. It can only be observed after rapid intravenous injection of ammonium salts, because otherwise the ion is rapidly converted to urea.

Neuromuscular Action. Ammonium salts have a weak curare-like action on voluntary muscle. This can only be demonstrated when high concentrations are applied experimentally to nerve-muscle preparations. Although this action has no therapeutic application, it is of interest because the organic quaternary ammonium bases, such as curare and choline, possess this curariform property to a much greater degree.

Acidosis and Diuresis from Neutral Ammonium Salts. Following the absorption of neutral salts of ammonia such as the chloride and nitrate, the conversion of the ammonium ion to urea leaves an excess of anion in the extracellular fluid. This may result in a severe acidosis if the dose of salt has been large. Acid-forming ammonium salts are markedly diuretic and are employed for this purpose (page 630). In the presence of inadequate renal function, the administration of ammonium salts is contraindicated because of the danger of an uncompensated acidosis.

Expectorant Action. The ammonium ion has an expectorant action and its salts are extensively used for this purpose (page 815).

Local Actions. Solutions of ammonia vapor (ammonium hydroxide) are local irritants. When applied to the skin in low concentration they have a rubefacient action and in high concentrations are vesicant. Ammonia gas is very irritating, but when inhaled in dilute form it can reflexly stimulate the medullary respiratory and vasomotor centers through irritation of the sensory endings of the trigeminal nerve. High concentrations of ammonia vapor are injurious to the lungs and death may result from pulmonary edema. Long exposure to low concentrations of ammonia may lead to chronic pulmonary irritation. The maximum concentration of ammonia vapor which can be tolerated without harmful effect is probably less than 250 parts per million.

High concentrations of neutral ammonium salts are irritating to the gastric mucosa but this is probably no more than a non-specific salt action. When systemic effects are desired, ammonium salts may be prescribed in solution but are best given in enteric-coated tablets.

Toxicology. The central actions of the ammonium ion are never seen in human beings for its salts are always given by mouth. In the event that the acidosis following the administration of ammonium salts becomes severe it can be controlled by the administration of a suitable solution of sodium lactate or sodium bicarbonate (page 592). The toxic properties of ammonia vapors have been discussed.

Preparations. *Ammonium Chloride,* U.S.P., B.P., consists of a white, crystalline, hygroscopic powder freely soluble in water. *Ammonium Nitrate* is not an official salt. It is a white, crystalline, hygroscopic powder freely soluble in wate *Ammonium Carbonate,* U.S.P., B.P., consists of a mixture of ammonium acid carbonate and ammonium carbamate. It consists of white, hard, translucent masses having an ammoniacal odor and taste. The salt is slowly soluble to the extent of 25 per cent in water.

Therapeutic Uses. The use of ammonium salts as expectorants is discussed on page 815; the use as diuretics, on page 631. As a reflex stimulant, *Aromatic Spirits of Ammonia,* U.S.P., is often employed. It is given by mouth in a dose of two cc, well diluted in water.

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CHAPTER 34

ANIONS: PHOSPHATES, IODIDES, FLUORIDES AND OTHER ANIONS

PHOSPHATES

The phosphate ion serves a variety of well-known functions in the body. These include the rôle of phosphate in the structure of bone, the part the ion plays in the acid-base equilibrium of the body fluids, its rôle in the intermediary metabolism of carbohydrate and its important part in the regulation of calcium metabolism and the calcium level of the blood. In addition, inorganic phosphate is the source material for the organic phosphates formed in the body. The phosphates have relatively few therapeutic uses, the average diet supplying an abundance of the ion. A defect in phosphate metabolism is likely to be the result of a more fundamental disturbance than is amenable to treatment with the phosphate ion itself. Nevertheless, there are a few occasions when phosphate salts are used in therapeutics and their pharmacological properties should therefore be understood.

Absorption, Fate and Excretion. Phosphates are absorbed from the gastrointestinal tract rather slowly. Absorption can be enhanced or retarded by altering certain conditions in the intestine. Large amounts of calcium in the bowel interfere with phosphate absorption by precipitating insoluble calcium phosphate. On the other hand, fat aids the absorption of phosphate by diverting calcium in the form of insoluble calcium soaps. As with calcium, an acid reaction in the duodenum favors the absorption of phosphate. The phosphate which is absorbed from the intestinal tract is excreted mainly by the urine and there is little reason to believe that phosphates are excreted into the intestine. It is thought that most of the phosphate found in the feces represents unabsorbed phosphate salts. Under ordinary conditions about two-thirds of the phosphate ingested in the diet is excreted in the urine. The rôle of the parathyroid hormone in the excretion of phosphates is discussed elsewhere.

After absorption, phosphates circulate in the blood mainly as sodium salts—the disodium salt (sodium alkaline phosphate, Na_2HPO_4) and sodium biphosphate (sodium acid phosphate, NaH_2PO_4). The pH of the blood controls the relative proportion of the two salts. At the normal pH (7.4), approximately 80 per cent of the blood phosphate exists as the basic salt and the remainder as the acid salt. The phosphate buffer system is very efficient, but there is not a sufficiently high concentration of phosphate in the blood for it to be of great physiological importance.

In the excretion of phosphate, however, an appreciable amount of base is saved for the organism. In the normally acid urine the phosphates are present as acid salts. The conversion of basic to acid phosphate probably takes place in the kidney, and as a result sodium salts are returned to the circulation, as illustrated in the following reaction:

$$Na_2HPO_4 + H_2CO_3 \longrightarrow NaH_2PO_4 + NaHCO_3$$

Thus, for every molecular weight that is changed from the basic phosphate to the acid phosphate, an equivalent of base is conserved for the body.

Actions of the Phosphate Ion. Once phosphate gains access to the body fluids and tissues, it exerts little pharmacological effect. If the ion is introduced into the gastro-intestinal tract, the absorbed phosphate is rapidly excreted. If large amounts are given by this route, much of it may escape absorption. This leads to a cathartic action and the phosphate salts are thus employed as mild laxatives. The ingestion of large amounts of sodium acid phosphate lowers the pH of the urine. If phosphate salts are introduced intravenously in high concentration they may prove toxic. Toxicity results from reducing the concentration of Ca^{++} ions in the circulation and the symptoms are those of hypocalcemia.

Organic Phosphates. Organic phosphates are generally distributed throughout the body. They include such compounds as lecithin, nucleins, cephalin, hexose phosphates, phosphocreatin, etc. At one time it was believed that the feeding of phosphate in the organic rather than the inorganic form resulted in much better assimilation of phosphorus and this misconception still persists. It is now known that the organism can utilize perfectly well inorganic phosphate for the formation of complex organic molecules, just as it can utilize inorganic iron for hemoglobin formation. The presence of high amounts of phosphorus in nervous tissue has fostered the erroneous belief that phosphates are good "nerve tonics," especially if given in the organic form. Consequently, expensive but useless preparations of organic phosphates are on the market.

Hypophosphates. These compounds represent another therapeutic tradition from the last century. Hypophosphoric acid has the structure HPH_2O_2. Various hypophosphate salts, often in combination with quinine and strychnine, enjoy unwarranted reputations as tonics.

Elemental Phosphorus. Elemental phosphorus has no uses in clinical medicine but is important in that it is frequently the cause of acute or chronic poisoning. The element occurs in two forms, yellow phosphorus and red phosphorus. The latter is non-toxic due to the fact that it is insoluble and non-volatile. Yellow phosphorus, however, forms a colloidal solution in water and is also volatile. Poisoning from it occurs in industry from the breathing of fumes and also from accidental ingestion. In former years, matches were tipped with yellow phosphorus and poisoning, especially among children, was common. This practice is now prohibited by law and the occasional case of phosphorus poisoning arises from the use of the element in rodent exterminators. As little as 15 mgm of yellow phosphorus can produce untoward symptoms and 60 mgm have been known to cause death.

Symptoms of Poisoning. The first symptoms following the ingestion of phosphorus are due to the local gastro-intestinal action of the element. They consist of abdominal pain and burning, nausea, vomiting and diarrhea, and may be immediate or delayed for several hours. The breath and vomitus have a characteristic garlic odor, and the vomitus is luminous. If the patient does not succumb to shock from the immediate effects of the phosphorus, there ensues a symptom-free period of from one to three days following which the systemic effects of the element become evident. Phosphorus is toxic to glands and muscles and especially so to the liver and the heart. The onset of the second stage of poisoning is heralded by nausea and protracted emesis producing a blood-streaked vomitus, diarrhea and abdominal tenderness in the region of the liver. The liver undergoes acute degeneration which may be quickly followed by atrophy. The accompanying metabolic disturbance results in pruritus, jaundice, the urinary excretion of amino acids and poor utilization of carbohydrate. The clotting of blood is affected (page 1296), and this coupled with direct damage to the walls of the blood vessels may result in ecchymoses and petechiae of the skin and hemorrhages in the mucous membranes and viscera. The kidney is injured as is evidenced by oliguria and the presence of casts and red blood cells in the urine. The urine is phosphorescent. Cardiovascular collapse results both from the metabolic disturbances and the direct toxic action of phosphorus on the heart muscle and blood vessels. Death usually follows a period of delirium or coma.

Chronic exposure to small amounts of phosphorus results in poisoning characterized by necrosis of bone, usually in the lower and upper jaw and the neighboring facial bones. There may be an accompanying cirrhosis of the liver and damage to the kidney.

Treatment. Every attempt should be made to prevent the absorption of orally ingested phosphorus. Gastric lavage should be performed even if the patient is first seen several hours after the poison has been taken. A suitable chemical antidote is copper sulfate (0.25 gram in a glass of water) which acts to envelop the phosphorus particles with an insoluble coating of copper phosphide. Oxidizing agents such as potassium permanganate (1:1000 solution) or hydrogen peroxide (two per cent of the official preparation) may aid the conversion of elemental phosphorus to harmless oxidation products. Following gastric lavage, a cathartic of magnesium sulfate should be given to cleanse the bowel of phosphorus, the element being but slowly absorbed. The remaining therapy is purely symptomatic and should include measures to prevent shock and acidosis, the administration of large amounts of fluid, glucose and electrolytes, adequate calcium and a diet high in carbohydrate. The clotting defect may be related to a low prothrombin content of the blood as is the case in liver damage due to other hepatotoxic agents. If the prothrombin content of the blood is found to be low, the hemorrhagic diathesis may be benefited somewhat by the administration of vitamin K.

Local phosphorus burns should be thoroughly washed with a one per cent solution of copper sulfate and then treated like other burns.

Preparations. Only the preparations of inorganic phosphates are worthy of mention. *Calcium phosphate* and *sodium phosphate* are described elsewhere. *Sodium Biphosphate* (*Sodium Acid Phosphate*), U.S.P., B.P., is a colorless, odorless, water-soluble crystalline powder with an acid, saline taste. *Phosphoric Acid,* U.S.P., B.P., is a colorless, syrupy liquid which is prescribed in the form of *Diluted Phosphoric Acid,* U.S.P., B.P., which is a solution containing 10 per cent phosphoric acid by weight. It should be further diluted before administration.

Therapeutic Uses. The phosphates are of limited therapeutic usefulness. Sodium biphosphate may be employed when it is desired to render the urine acid. As an example may be cited the practice of prescribing sodium biphosphate during therapy with methenamine to insure the efficacy of the latter as a urinary antiseptic (page 837). The dose usually employed is 1.0 to 2.5 grams every four hours, midway between the doses of methenamine. Sodium phosphate may be used as a mild cathartic (page 807). Phosphoric acid is of value in the treatment of lead poisoning (page 730).

Pathological Conditions Associated with a Disturbance in Phosphate Metabolism. There is a variety of diseases in which a defect in phosphate metabolism is a feature. These conditions can be little more than enumerated for they usually call for more fundamental therapy than the administration of phosphate.

Rickets is often associated with an abnormality in phosphate metabolism. Experimentally rickets can be produced either by a diet low in calcium and high in phosphorus or *vice versa.* Frequently, in rickets unaccompanied by convulsions, analysis of the blood reveals a phosphorus rather than a calcium deficit. On the other hand, rickets may occur when the blood phosphate is at a high level. In such an instance, it is usually associated with a hypocalcemia. The lack of vitamin D in the diet affects the absorption of both calcium and phosphate. Deficiency in this vitamin causes most cases of rickets, and therefore therapy requires emphasis on the administration of vitamin D rather than on the inorganic constituents which form bone. *Osteomalacia,* like rickets, may be associated either with a low blood calcium or phosphate level. In *hypoparathyroidism* with its attendant hypocalcemia, there is usually an increase in the concentration of blood phosphate. The opposite is true during hyperfunction of the parathyroid glands. *Nephritis* is usually associated with changes in the blood phosphate level. An increase in concentration of phosphate is evidence of renal failure, and the accumulation of phosphate may contribute to the loss of bicarbonate and the acidosis of advanced nephritis.

In the conditions enumerated, analysis of the calcium and phosphate levels of the blood may help in the diagnosis and in following the course of the disease. Therapy in these cases, however, rarely demands phosphate medication.

IODIDES

There are numerous iodine-containing compounds of pharmacological interest. These include the element iodine, substances yielding elementary iodine, the inorganic iodides and iodine-containing organic compounds. Iodine compounds have many unrelated actions and are used in a number of very specialized ways. Consequently, the pharmacology of iodine has been largely subdivided and the various iodine-containing drugs are taken up with primary regard to their therapeutic applications. Reference to the index will direct one to the discussion of the antiseptic action of iodine, the use of iodides as expectorants, the employment of iodides in syphilis and other granulomatous diseases and the relation of iodides and organic iodine-containing compounds to the metabolism and diseases of the thyroid gland. In this section, discussion will be limited to the general pharmacological aspects of the iodides, their toxicology, and a few miscellaneous applications.

Absorption, Distribution and Excretion. The iodides are absorbed from most mucous membranes. The claim that iodides are readily absorbed from the stomach may be questioned for few if any inorganic salts can penetrate the gastric mucosa.

After absorption, iodide is distributed in exactly the same manner as chloride and bromide. In other words, its distribution is entirely extracellular except for its penetration into the red blood cell (Wallace and Brodie, 1938, 1939). This fact negates much of the earlier work which indicated that the iodide ion was taken up selectively by pathological tissue, as for example, by tuberculous and carcinomatous lesions. After equilibration, the amount of iodide in the serum is an index to its concentration in all other extracellular fluids.

The iodide ion is readily excreted by the kidney. It is highly probable that the kidney excretes iodide preferentially over chloride, for most of the ion is lost from the body within 24 hours. If the kidney did not distinguish between these halogens, the excretion of iodide would be a slow process, as is the excretion of bromide. However, the excretion of iodide is influenced to some extent by the other halides, because the elimination of the ion may be somewhat hastened by the administration of large amounts of chloride. There is very little retention of iodide and that which remains in the body is in organic combination. In addition to its presence in the urine, iodide can be detected in all the other extracellular body fluids. It appears in the gastric secretion as hydriodic acid and can be found in saliva, perspiration, bile, milk, effusions, etc.

Pharmacological Actions. The iodides exert few marked pharmacological actions. Even after intravenous administration of large amounts, there is no observable specific response. Neither the central nervous system nor the circulation is affected. After oral administration, the iodides may cause local gastro-intestinal irritation but this is characteristic of most salts. The acid gastric juice may liberate free iodine from iodide salts. Under such conditions, the enzymatic processes within the stomach may be inhibited.

The action of iodide on inflammation and diseased tissue is imperfectly understood, and yet this action is the accepted basis for many of its therapeutic applications. The halide is said to have a "histolytic effect" and to aid in the "reabsorption of inflammatory lesions." In tertiary syphilis, the ion provokes a favorable reaction leading to the resolution of gummatous tissue. This may be a response to some type of irritation to which pathological tissue is unusually susceptible. For example, in tuberculous patients, iodides arouse irritative reactions and may even activate a dormant lesion. In tuberculous patients, therefore, iodides are contraindicated.

Toxicology. *Acute poisoning* from an initial dose of the iodides is relatively rare and even after intravenous injections reactions are seldom seen. An occasional individual, however, shows a marked sensitivity and therefore before iodide salts are given by the intravenous route, the tolerance of the individual should be determined. The onset of acute iodide poisoning may occur immediately or several hours after the administration of the salt. Angioneurotic phenomena are the outstanding symptoms and edema of the larynx may lead to suffocation. There also may occur multiple cutaneous hemorrhages of the skin and mucous membranes but these are quite rare.

Chronic iodide poisoning or *iodism* is a phenomenon which is likely to attend iodide medication. There is no means of predicting which patient will react unfavorably, and an individual may vary in his sensitivity to the drug from time to time. So capricious is the response to iodides that the symptoms of iodism resulting from a small dose may disappear if the dose is doubled. Eventually, iodism will occur in all individuals if the dose level is sufficiently high.

The symptoms start with an unpleasant brassy taste and burning in the mouth and throat and soreness of the teeth and gums. Increased salivation is noted. Coryza, sneezing, and irritation of the eyes with swelling of the eyelids are commonly observed. The person with a mild form of iodism presents the picture simulating an acute "head cold." The patient often complains of a severe headache which originates in the frontal sinuses. Irritation of the mucous glands of the respiratory tract leads to a productive cough. Excess transudation in the bronchial tree may lead to pulmonary edema. In addition, the parotid and submaxillary glands (iodide mumps), the pharynx, larynx and tonsils may show inflammatory reactions. Skin lesions are common. They usually are mild, acneiform in character and distributed in the seborrheic areas (chest and face). Rarely, a severe and sometimes fatal skin eruption (iododerma) may occur after the prolonged use of iodides. The lesions are bizarre, resemble those caused by bromides, and as a rule involute quickly when iodides are withdrawn. Gastric disturbance is common, diarrhea may occur, and the latter may be bloody. The chronic administration of iodides may lead to cachexia and depression. Fever is sometimes noted during iodism.

The cause of iodism is unknown. Many theories have been advanced to explain it but none has experimental support. It has been said that iodides affect the colloidal equilibrium of body fluids, on the meager basis that iodides will increase slightly the sedimentation rate of the red blood corpuscles. Others consider iodism to be an anaphylactic response. There are also claims that iodides increase autolysis and proteolytic processes. Still another suggestion is that permeability of blood vessels is increased. Some consider free iodine to be the toxic agent, but it is doubtful whether in the body free iodine is ever liberated from the iodide salts. The symptoms and therapy of acute iodine poisoning are described on page 844.

Treatment of Iodism. Fortunately, the symptoms of iodism will disappear spontaneously within a few days after stopping iodide medication. Treatment therefore includes no more than stopping the drug and using supportive measures as determined by the particular symptoms. Abundant fluid and increased sodium chloride intake may be of assistance in hastening iodide elimination. Iodism is only rarely fatal (Barker and Wood, 1940).

Preparations. The preparations of iodides may be grouped in three classes, as follows: (1) the inorganic iodides, (2) the organic iodides which yield the iodide ion, and (3) organic iodides which are used solely as contrast media in roentgenography.

Inorganic Iodides. The important inorganic sources of the iodide ion are *Sodium Iodide,* U.S.P., B.P. and *Potassium Iodide,* U.S.P., B.P. Both are white, crystalline salts highly soluble in water. The iodides are commonly administered in the form of their solutions. *Compound Solution of Iodine (Lugol's Solution),* U.S.P., contains five per cent elemental iodine and 10 per cent potassium iodide in aqueous solution. Potassium iodide alone is often prescribed as the saturated solution which contains about one gram of potassium iodide per cc. *Diluted Hydriodic Acid,* U.S.P. (10 per cent hydriodic acid) is commonly employed in the form of *Syrup of Hydriodic Acid,* U.S.P., (1.4 per cent hydriodic acid) which is used as a vehicle for expectorant drugs.

Organic Iodides. The organic iodides were introduced into therapy because of their sustained action. They are but slowly excreted and during their sojourn in the body liberate iodide. Most of the preparations consist of iodized proteins, iodized oils or fatty acids, or simpler iodine-containing aliphatic compounds. The iodized proteins are broken down in the gastro-intestinal tract and the iodide ion is absorbed as such. The other types of preparations probably liberate the iodide ion after absorption. In addition to their more sustained action, it has been claimed that the organic iodides are less irritating to the gastro-intestinal tract and do not cause the undesirable symptoms of iodism. They are undoubtedly less irritating than the inorganic preparations. However, a product incapable of causing iodism is *pari passu* one of low therapeutic efficiency because iodism is apparently a toxic extension of the pharmacological activity of the iodide ion. A unique application of the organic iodides is as contrast media in roentgenography.

The following are the organic iodide preparations which are either official or are accepted for inclusion in N.N.R.

Iodalbin, N.N.R. This is a compound of iodine and blood albumin. It contains approximately 21.5 per cent iodine and consists of a reddish-colored powder which is insoluble in water. It is employed orally as a substitute for inorganic iodides, is marketed in 0.5 gram capsules and its dose is from 0.3 to 0.6 gram.

Iodo-casein, N.N.R. This is a compound of iodine and milk casein. It contains approximately 18 per cent iodine and consists of a yellowish-brown powder which is insoluble in water. It is employed orally as a substitute for inorganic iodides. It is marketed in tablets containing 0.3 gram and its dose is 0.3 to 1.3 grams, as indicated. For the prophylaxis of goiter, chocolate tablets containing the equivalent of 0.01 gram of iodine are available (for discussion of dosage, *see* page 1162).

Iothion, N.N.R. This compound is diiodohydroxypropane, $CH_2ICH(OH)CH_2I$. It contains 77 to 80 per cent iodine and consists of a yellowish oily liquid which is insoluble in water. It is marketed in an alcohol, glycerin or ointment base and is applied directly to the skin for systemic absorption. It is employed as a substitute for inorganic iodides.

Siomine, N.N.R. This compound is hexamethylenetetramine tetraiodide, $(CH_2)_6N_4I_4$. It consists of a red powder containing 78.5 per cent iodine. It is employed orally as a substitute for inorganic iodides, is marketed in capsules containing from 0.03 to 0.3 gram and its dose is the same as that of potassium iodide.

Chloriodized Rapeseed Oil, N.N.R. This is a halogenated addition product of rapeseed oil and contains from 24 to 26 per cent iodine and seven to eight per cent chlorine. It consists of a yellow semiviscous oil and is marketed in ampules containing 20 cc of a 25 per cent emulsion in acacia solution. It is employed as a roentgenographic opaque medium in urography and the dose employed depends upon the size of the cavity to be visualized.

Iodostarine, N.N.R. This is an iodine addition product of tariric acid, $C_{18}H_{32}I_2O_2$. It contains 47.5 per cent iodine and occurs as a white crystalline solid. It is marketed in tablets containing 0.25 gram each and in chocolate tablets containing the equivalent of 0.01 gram of iodine. The compound is employed orally as a substitute for inorganic iodides.

Lipiodol, N.N.R. Lipiodol is an iodized poppy-seed oil which contains 40 per cent iodine. The compound occurs as a thick viscous oily liquid. It is marketed in ampules containing 0.5 gram. The drug is employed both as a substitute for inorganic iodides and as a contrast medium for roentgenography. The oral dose for the former purpose is 1.0 to 2.5 grams daily, taken after meals; for the latter, one to five cc or more of the oil, depending upon the purpose to be served, are injected.

Lipiodol Radiologique Ascendant, N.N.R. This is an iodized poppy-seed oil containing 10 per cent iodine. It is a yellow oily liquid which is employed as a contrast medium of lesser density than the spinal fluid for the recognition of intradural tumors.

Lipoiodine, N.N.R. This compound is ethyl diiodobrassidate, $C_{21}H_{39}I_2COOC_2H_5$, and contains 41 per cent iodine. It is marketed in 0.3 gram tablets and in 10 cc bottles containing a 60 per cent solution of the drug in sesame oil. The compound in tablet form is employed orally as a substitute for inorganic iodides and the solution in oil is used as a contrast medium in roentgenography. The doses are 0.3 to 0.6 gram and five to 20 cc, respectively.

Oridine, N.N.R. This preparation is the calcium salt of the iodized fatty acids of cottonseed oil. It contains 23 to 25 per cent iodine and consists of a light brown powder, insoluble in water. It is employed as a substitute for inorganic iodides, is marketed in tablet form and its oral dose is three times that of potassium iodide.

Riodine, N.N.R. This is a 66 per cent solution in oil of an iodine addition product of castor oil. It contains 17 per cent iodine and is marketed in pearls containing 0.2 gram. It is employed orally as a substitute for inorganic iodides in the dose of 0.4 to 1.2 grams per day.

Stearodine, N.N.R. This compound is calcium iodostearate, $Ca[CH_3(CH_2)_7CHI(CH_2)_8COO]_2$. It contains from 26 to 28 per cent iodine and consists of a cream colored solid which is insoluble in water. It is marketed in tablets containing the equivalent of 0.01 gram of iodine and is used orally in the prophylaxis and treatment of goiter as a substitute for inorganic iodides.

Calcium Iodobehenate, U.S.P. Calcium iodobehenate, $(C_{21}H_{42}ICOO)_2Ca$, contains 23.5 per cent iodine and occurs as a white or yellowish powder which is insoluble in water.

It is marketed in tablets, and is employed orally as a substitute for inorganic iodides in the dose of from one to three grams daily.

Diodrast, N.N.R. Diodrast is a water-soluble iodine-containing compound which consists of a loose chemical combination of diethanolamine, $NH(CH_2CH_2OH)_2$, and 3, 5-diiodo-4-pyridone-N-acetic acid, $C_5H_2OHNI_2CH_2COOH$. It contains approximately 49.8 per cent iodine. Diodrast is used as a contrast agent for intravenous urography. It is administered in 35 per cent solution in the adult dose of 20 cc (seven grams of diodrast). Injections should be made slowly. Systemic reactions occasionally occur and consist chiefly of flushing of the skin with a sense of warmth. Less frequently, transient nausea and vomiting, erythematous eruptions, respiratory distress and cyanosis may develop. The symptoms usually subside within a few minutes to an hour but in rare instances the skin eruptions may persist for several days. The use of the drug is contraindicated in patients with severe liver disorders, nephritis, tuberculosis or hyperthyroidism, and great care is to be exercised in cases of uremia. Also, the drug may cause a fall in blood pressure for a period of two hours and caution must be observed in cases where such a reaction is undesirable.

Neo-iopax, N.N.R. This is another water-soluble iodine-containing compound which is used as a contrast medium for intravenous urography. Chemically, the compound is the disodium salt of N-methyl-3, 5-diiodo-chelidamic acid, $NaOOC{\cdot}C_5ONI_2{\cdot}CH_3COONa$. It contains 51.1 per cent iodine. The adult dose is 20 cc of a solution containing 15 grams of the drug. There may be transient radiating pain attending the injection but it occasionally persists for a variable period. The contraindications to neo-iopax are the same as for diodrast. The compound is marketed in 10 and 20 cc ampules containing 7.5 and 15 grams, respectively.

Skiodan, N.N.R. This is the sodium salt of mono-iodomethanesulfonic acid, $CH_2I{\cdot}SO_3Na$. It is used for the roentgenographic visualization of the urinary tract and is given either by intravenous injection or by direct injection of the aqueous solution into the renal pelvis through a ureteral catheter. The intravenous dose for adults is 20 to 40 grams in 100 cc of sterile water, and for retrograde pyelography 100 cc of a 10 or 20 per cent solution are injected. Cystograms may be made with three or five per cent solutions.

Therapeutic Uses

"Wenn man nicht weiss Wieso und Warum,
Dann gibt man Jodkalium."

This couplet expressively summarizes the status of iodide therapy. The iodides have been employed empirically in a wide variety of diseases too numerous even to be fully listed. As examples, one might cite their use in the treatment of encephalitis, essential hypertension, portal cirrhosis, thromboangiitis obliterans, etc. Results have not been sufficiently favorable to warrant their discussion. In many instances, however, the iodides are effective, the salts being of particular value in *actinomycosis, syphilis* and *hyperthyroidism,* for the *prophylaxis of goiter,* and as an *expectorant* (*see* Index).

The organic iodides are widely employed as a contrast medium in roentgenography. For this purpose there are two types of preparations utilized, the iodized oils and the water soluble iodine-containing compounds.

The early history of the use of iodized oils in roentgenography was reviewed by Lindskog and Tennant (1939), and the status and dangers of these compounds were presented by the Council (1932). The iodized oils are used for injection into body cavities. The injection of the oils is essentially a surgical procedure involving more or less risk which should be weighed against the advantages to be obtained. The following precautions have been listed by the Council: (1) Oils that have aged and darkened beyond their original color should never be used. (2) Subarachnoid injection should be avoided, at least until all other means of diagnosis have been exhausted. (3) Intratracheal and intrapleural injections should be avoided in tuberculosis of the respiratory organs and also when restriction of the respiratory area would be contraindicated. (4) The injection pressure should be carefully controlled in order not to lacerate the tissue. (5) Intra-uterine injections should be made only under fluoroscopic observation. (6) Iodized oil should not be used for renal pyelography, except in the form of an emulsion, and the injection should be stopped if pain is felt.

The water-soluble organic iodides are injected intravenously, are excreted by the kidney, and during the course of their excretion serve as a contrast medium for roentgenography of the urinary tract. The reactions attending their injection have been discussed. The optimum time for taking roentgenograms is from five to 15 minutes after the injection of diodrast and from 20 to 30 minutes after the injection of neo-iopax. In the event that renal function is impaired, a longer wait is necessary in order that an adequate concentration of the drug may be present in the urinary tract.

FLUORIDES

The fluorides are not used in therapeutics and are of interest chiefly because of their toxic properties. Fluorides are widely distributed in nature and easily gain access to plants from the soil. Animals obtain this ion from plants and drinking waters. Certain foods are particularly contaminated with fluorides. For example, fluoride may be a contaminant of the phosphate contained in baking powder.

Absorption, Distribution and Excretion. Fluoride is readily absorbed from the intestinal tract but differs from other halogens in its slow excretion. Consequently, it accumulates in the body. Chronic fluoride poisoning can be produced easily in animals and is by no means unknown in man. The fluoride ion is distributed in a characteristic fashion in the animal organism. The greatest amounts are found in bones and dental enamel. Other organs have a uniformly low content.

Gettler and Ellerbrook (1939) devised accurate quantitative methods for the determination of fluorine. In normal human tissues they find the content of fluorine in the bones and teeth to be from 10 to 30 mgm per 100 grams; in soft tissue, 20 to 80 γ per 100 grams. In fatal acute cases of fluoride poisoning, the tissues contain 140 to 1600 γ per 100 grams.

The deposition of fluoride in bone is thought to result from the formation of insoluble calcium fluoride at that site. It is interesting to note that the concentration of fluoride has been used to estimate the geological age to which a fossil bone belongs. Fluoride washed from the soil is deposited in the buried bones and accumulates there during the course of the centuries.

Biological Rôle of Fluoride. Although the fluoride ion occurs in all body tissues, there is no evidence that it serves a specific physiological function. It is probable that its presence is merely a reflection of its wide distribution in nature. Sharpless and McCollum (1933) fed animals diets low in fluoride and have observed no deleterious effects.

Pharmacological Actions. These can be classified as toxic. Fluoride is a "general protoplasmic poison." The ion is bactericidal, inhibits enzymatic activity, diminishes tissue respiration and anaerobic glycolysis in excised organs, and decreases oxygen consumption and lactic acid production in muscle. It has also been claimed that fluoride decreases the oxygen consumption and carbon dioxide production in intact animals. Fluorides are also anticoagulants. This probably results from the precipitation of calcium, although there is some evidence that the ion may affect thrombin formation. In the laboratory, fluorides are valuable anticoagulants for blood when it is desired to stop all biological activity, such as glycolysis in erythrocytes.

Action on Metabolism. The action of the fluoride ion on the metabolic rate of mammals deserves separate consideration, for this action has been the subject of investigation and the basis of therapeutic application. For example, fluorides have been reported to be beneficial in hyperthyroidism, an effect believed by some to result from an enzyme-inhibiting action. Another view holds that thyroxin may be precipitated by fluorides. Subsequent investigations, however, show that fluorides neither decrease the metabolic rate of normal animals nor affect the activity of administered thyroid (Seevers and Braun, 1935; Phillips, 1936).

Acute Poisoning. Acute fluoride poisoning is not rare and usually results from the accidental ingestion of insecticidal fluoride salts. Initial symptoms are referable to the local action of fluoride on the gastro-intestinal mucosa. Salivation, nausea, abdominal pain, vomiting and diarrhea are frequent. Systemic symptoms are varied and severe. The nervous system is affected and epileptiform convulsions occur. The blood pressure falls due to central vasomotor depression and to a direct toxic action of fluoride on heart muscle. The respiratory center is first stimulated but eventually depressed and death results either from respiratory paralysis or cardiac failure. The toxic dose of sodium fluoride for human beings is probably about five grams.

Treatment is mainly symptomatic. The administration of chemical antidotes to precipitate unabsorbed fluorides in the gastro-intestinal tract is helpful if the patient is seen sufficiently early. Soluble calcium salts are most effective in this regard. If none is quickly available, large quantities of milk may be given.

Chronic Poisoning. Chronic fluoride poisoning is a public health problem. It occurs in several sections of the United States where the fluoride content of the water is unusually high. The feeding of fluorides at a daily dose level of 15 to 150 mgm per kg will produce symptoms of chronic poisoning in mammals. Growth is retarded, the estrus cycle and reproduction are inhibited, and histological changes occur in the pituitary and thyroid glands. The most significant finding, however, is in the teeth.

Mottled Enamel. Black and McKay (1916) were the first to report a dental imperfection which they termed "mottled teeth." They recognized this affliction to be endemic and in later publications McKay (1918, 1925) came to the conclusion that mottled teeth were related to the water supply. Meanwhile, workers experimenting in the field of chronic fluoride poisoning observed structural defects in the teeth of animals ingesting fluoride salts. These defects were studied especially in the rat where the changes are obvious. The enamel loses its characteristic normal tint and becomes dull white. The incisors become brittle and loose in their sockets. In the rat, the lower incisors fracture spontaneously and no longer remain in apposition to the upper incisors. The latter continue to grow, curve upward and attain a characteristic shape. Histological study reveals imperfect calcification of the enamel rods and a deficiency of intercement substance.

The mechanism by which fluorides cause dental imperfection is not clear. It is estimated that the daily ingestion of 0.1 to 0.15 mgm of fluoride per kg of body weight during the time that enamel of the permanent teeth is being laid down will lead to imperfections. It is known that fluorides will interfere with normal calcium metabolism but the amount cited is insufficient to cause noticeable disturbance in the calcium balance. Neither does the feeding of calcium prevent this condition. DeEds (1936) concluded, therefore, that the action of fluoride on enzymes is the basic cause for the dental defects. He believes the action to be one on phosphatase and has demonstrated that low concentrations of fluoride decrease the activity of bone phosphatase.

Preparations and Uses. There are no official fluoride preparations. Sodium fluoride and sodium fluosilicate (Na_2SiF_6) are the salts commonly used as insecticides. There is no established therapeutic use for fluoride. At one time it was used as a food preservative but the ion is much too toxic to be employed for this purpose.

CHLORIDES

The chloride ion (Cl^-) has little pharmacological action. It is the chief anion of the extracellular fluid and, due to the fact that apparently its major function is an osmotic one, it has been termed "osmotic stuffing." The chloride is an essential ion in that the osmotic function which it performs cannot be discharged by any other anion.

An excess of chloride ion in the extracellular fluids causes acidosis. It is occasionally desired to produce acidosis and this is conveniently accomplished by the administration of ammonium chloride (page 630). Hydrochloric acid is another form in which the chloride ion is administered (page 791).

Chlorides are extensively employed in the form of the neutral salt, *Sodium Chloride,* U.S.P., B.P., which is the one salt that contains the two major ionic components of the extracellular fluids. Sodium chloride is widely used in conditions characterized by extracellular dehydration (page 584), and in disturbances of acid-base balance. In isotonic concentration, it is non-irritating to tissues and can be administered intravenously or subcutaneously. Isotonic solutions of the salt are also valuable for irrigations and can be used for gastric or colonic lavage without the risk of electrolyte depletion entailed by the use of plain water.

SULFATES

The sulfate ion does not penetrate cell membranes readily and its pharmacological properties result from this relative impermeability. When given orally, the sulfate ion is slightly absorbed from the gastro-intestinal tract. Consequently sufficient water is held in the intestinal lumen to render the contents isotonic, and thus sulfate salts act as saline cathartics (page 807).

The sulfate ion, upon injection, remains in the extracellular fluid. Here it has no pharmacological action. The ion, however, is rejected by the renal tubule and as a result sulfate salts are powerful osmotic diuretics (page 627). They are not used clinically as diuretics, however, inasmuch as parenteral administration is required. The sulfate salts employed in medicine for the action of the anion are *Magnesium Sulfate,* U.S.P., B.P. and *Sodium Sulfate,* U.S.P., B.P. Both are employed chiefly as saline cathartics.

NITRATES

The nitrate ion (NO_3^-) has no specific pharmacological action and has few therapeutic uses. The nitrate salts are diuretic and both potassium and ammonium nitrate are used for this purpose (page 630). There is evidence that the nitrate ion is converted to the nitrite ion by the action of bacteria in the intestine, and thus bismuth subnitrate is occasionally employed for its potential nitrite action (page 563). Likewise, the burning of nitrates leads to the formation of nitrites and this procedure has been used in order to obtain the antispasmodic action of the nitrite ion for the relief of asthma (page 563).

The nitrate salts are irritating to the gastro-intestinal tract, and cause more or less nausea and gastric distress. Soluble salts of nitrates should therefore be administered in enteric-coated tablets rather than in solution.

LACTATES

The lactate ion ($CH_3CHOHCOO^-$), like the acetate, has no specific pharmacological action. The anion is metabolized and therefore sodium lactate is often given intravenously as a potential source of base (page 584). Calcium lactate (page 604) is a convenient form in which to administer calcium without the danger of producing acidosis.

ACETATES

The acetate (CH_3COO^-) ion has no specific pharmacological action and the acetate salts are used in medicine chiefly for the purpose of introducing a particular cation. The acetate ion is burned in the body and the cation is left in combination with available bicarbonate. Thus the acetate salts can be used orally to compensate for milder grades of acidosis. They also possess a diuretic salt effect. Their expectorant action is discussed on page 816. Official preparations include *Sodium Acetate,* U.S.P., *Potassium Acetate,* U.S.P., B.P. and *Solution of Ammonium Acetate,* U.S.P., B.P. The acetate salts are water-soluble, white crystalline powders with a sharp saline taste.

OXALATES

The oxalate ion is toxic because it precipitates ionized calcium. The symptoms of oxalate poisoning are those of hypocalcemia (page 601) and they respond to the intravenous injection of calcium salts. Oxalic acid is also a powerful local irritant, but in cases of poisoning the administration of basic substances is contraindicated because the soluble sodium oxalate is readily absorbed and the systemic actions of the oxalate ion are more dangerous than the local effects of the acid. Rather, calcium salts should be given.

The oxalate salts are extensively used in laboratory procedures to prevent the coagulation of blood *in vitro.* They accomplish this by precipitating ionized calcium. *In vivo,* however, small amounts of oxalate apparently shorten rather than prolong the coagulation time. Steinberg and Brown (1939), investigating the composition of plant extracts which were capable *in vivo* of reducing clotting time in experimental animals, identified the active substance as oxalic acid and succeeded in duplicating the effects of the extracts with pure oxalic acid. Preliminary clinical reports have appeared on the efficacy of the oxalates in reducing the coagulation time of the blood. The mechanism of action is not known. Foster (1940) has questioned the ability of oxalates to reduce coagulation time.

Certain plants contain appreciable amounts of oxalate salts. Rhubarb is one of this group. The edible stalks contain a relatively low concentration, but the content of the leaf is high. Ingestion of large amounts of oxalate-containing vegetables or berries may result in oxaluria, hematuria and renal colic.

TARTRATES

The tartrate ion ($COO^-CHOHCHOHCOO^-$) is absorbed with difficulty from the gastro-intestinal tract and therefore tartrate salts may safely be employed as saline cathartics (page 807). If high concentrations of the tartrate ion gain access to the circulation, renal damage results, and tartrates may be employed experimentally to produce renal tubular lesions. For this purpose, the salts must be given parenterally because intestinal absorption is too slow to enable a toxic amount to reach the circulation. The official tartrate salts are described elsewhere (*see* Index).

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SECTION VIII

DRUGS AFFECTING URINE FORMATION

CHAPTER 35

DIURETICS AND ANTIDIURETICS

Diuretics are drugs which promote the formation of urine; *antidiuretics* are drugs which suppress the formation of urine. Although there are many substances which may alter renal function, as, for example, almost any agent which affects the circulation, innumerable toxic substances, etc., the terms as defined are usually reserved for those drugs which have a major action on the kidney which is applicable clinically.

Drugs may affect renal function in a variety of ways. A clear understanding of the mechanism of action of diuretics and antidiuretics rests upon a comprehensive knowledge of renal function.

PHYSIOLOGICAL CONSIDERATIONS

According to present views, all the eventual constituents of the urine appear in the glomerular filtrate. The glomerular fluid is obtained from the blood by the process of diffusion and has been termed an ultrafiltrate of the serum. The filtering surface is the capillary bed of the glomeruli. The glomerular filtrate passes down the tubule and is subjected to the activity of the tubular cells. At this site, the elements of this ultrafiltrate may be completely reabsorbed, partially reabsorbed or completely rejected. Briefly, the excretion of urine is the combined result of glomerular and tubular activity and in the last analysis a diuretic or antidiuretic must influence one or both of these functions.

Glomerular Function. Functionally, the glomerulus of the kidney is little different from other capillary beds, and glomerular filtration is subject to the same physical laws which govern the transport of fluid, permeable ions and molecules across any capillary membrane. Its filtering force is the hydrostatic pressure of the blood. Opposed to this force is the osmotic pressure of the serum proteins which do not penetrate the normal glomerular membrane. All the blood constituents, with the exception of the proteins, lipids and cellular elements, gain access to the glomerular capsule. The concentration of the diffusible elements is practically the same in the glomerular filtrate as in the blood.

The glomerular capillary bed has two distinct features: (1) the efferent vessel is an arteriole rather than a venule, and (2) the capillary transudate is drained to the outside of the body and does not meet the usual resistance of tissue turgor. Glomerular filtration is therefore influenced by factors which do not affect other capillary beds.

The main factors which govern the glomerular filtration are the hydrostatic pressure of the blood and the opposing osmotic force of the nondiffusible serum proteins. The former has been roughly estimated at 60 per cent of the arterial pressure and the latter force is equivalent to approximately 20 mm of mercury. Thus, under normal conditions there is an appreciable head of pressure in the glomerulus, and the homeostasis of the body must be considerably disturbed before the rate of glomerular filtration is significantly changed. For example, systolic blood pressure must be reduced to a level of 40 mm of mercury before glomerular filtration ceases. It is not surprising, therefore, that results of investigations on the mechanism of action of diuretics and antidiuretics have minimized the importance of the rate of glomerular filtration. Theoretically, however, the rate of glomerular filtration may be altered by (1) the hydrostatic pressure within the glomerulus, (2) the osmotic pressure of the nondiffusible constituents of the blood, (3) the number of functioning glomeruli and rate of blood flow, and (4) back pressure from those structures which drain the glomerular filtrate to the outside. These factors must be considered in localizing the action of any diuretic or antidiuretic.

Tubular Function. If glomerular activity were the only mechanism regulating the rate of urine flow, it is conceivable that certain drugs might sufficiently affect filtration rate markedly to alter urine volume. The glomerular filtrate, however, is further subjected to the activities of the renal tubules. The rate of glomerular filtration has been determined to be more than 100 cc per minute. A normal adult excretes urine at the rate of one cc per minute over a 24 hour period. Thus 99 per cent of the glomerular fluid is normally reabsorbed by the tubules. The amount of fluid reabsorbed, however, is subject to variation, and under conditions of abnormal posterior pituitary function, as in diabetes insipidus, as much as 20 per cent may escape reabsorption. At this point the relative importance of tubular and glomerular function in relation to urine volume should be emphasized. If glomerular filtration rate remains constant, a decrease in the reabsorption of the glomerular fluid by the tubules from 99 to 98 per cent will double urine volume. Glomerular filtration, on the other hand, would have to be increased 100 per cent in the face of a constant percentage of reabsorption by the tubules in order to double urine volume. The changes in renal blood flow or effective filtration pressure necessary to accomplish this excretory feat exceed physiological probability.

In addition to reabsorbing water, the tubules normally reabsorb all the glucose which appears in the glomerular filtrate. Over 95 per cent of the electrolytes are also reabsorbed. It is obvious that with high rates of glomerular filtration and water reabsorption, failure to reabsorb the ions which form the extracellular fluids of the body would rapidly lead to a fatal depletion of these substances.

The tubules also have the function of excretion. According to present concepts, this is accomplished mainly by not reabsorbing substances in the glomerular filtrate which are destined for excretion. The ability of the tubules to reject urinary constituents varies. Thus 50 per cent of the urea filtered through the glomerulus diffuses back through the tubules, whereas little if any of filtered creatinine is reabsorbed.

An important concept to remember is that *the excretory activity of the tubule is influenced by the composition of the blood.* For example, reabsorption of the cation sodium diminishes when there is an excess of sodium in the blood. Also, an excess of a particular anion in the blood will result in its excretion in the urine accompanied either by fixed base or by ammonia formed in the kidney.

Another important factor to consider in the physiological basis of diuretic action is the *osmotic work of the tubules.* The mammalian kidney can elaborate a urine hypertonic to the blood, because water can be abstracted by tubular cells to form a *hypertonic* fluid in the tubular lumen. For example, the electrolyte concentration of the urine may be twice as great as that of the blood, and the urea concentration 80 times as great. *The osmotic pressure of the urine is limited, however, by the capacity of the tubular cells to do osmotic work. Thus when large amounts of excretory substances fail to be reabsorbed, their excretion must necessarily be accompanied by water, the reabsorption of which is prevented by the osmotic pressure of the fluid in the tubules.* The functional integrity of the posterior pituitary gland is necessary for the performance of osmotic work by renal tubules. The evidence suggests that the loops of Henle are the portions of the tubules responsible for this osmotic work.

DIURETICS

Classification of the Diuretics. The diuretics may be classified in five major groups and will be discussed in the following order:

I. Water

II. Osmotic Diuretics
  A. Neutral salts
    Sodium chloride
    Potassium chloride
    Potassium nitrate
  B. Acid-forming salts
    Ammonium chloride
    Ammonium nitrate
    Calcium chloride
  C. Osmotically active molecules
    Urea
    Glucose
    Sucrose
  D. Substances altering oncotic pressure
    Acacia

III. Xanthines
  A. Caffeine
  B. Theobromine
  C. Theophylline

IV. Mercurials
  A. Mercurous chloride
  B. Merbaphen
  C. Salyrgan
  D. Mercurin
  E. Mercupurin

V. Miscellaneous Diuretics
  A. Digitalis
  B. Desiccated thyroid
  C. Parathyroid extract

THE ACTIONS OF INDIVIDUAL DIURETICS

Water

Water is a true physiological diuretic. Although water is seldom considered as a drug, the forcing of fluid is a recognized therapeutic measure.

Mechanism of Diuretic Action. The mechanism of water diuresis is still debated. The bulk of evidence indicates that the posterior pituitary is a gland of internal secretion which regulates the excretion of water in mammals. In the absence of the posterior pituitary, marked disturbances in water metabolism occur.

After water administration, there are few changes in the circulation which can significantly increase the rate of glomerular filtration. Because water distributes itself through all the fluid media of the body, blood concentration and blood pressure are little affected by amounts of water which provoke considerable diuresis. One must therefore assume that decreased tubular reabsorption and not increased glomerular filtration is responsible for water diuresis.

There is increasing evidence that the concentration of posterior pituitary principle in the blood is the factor which controls the water-reabsorbing activity of the tubules. H. Smith (1937) discusses this evidence in detail. It points to a secretory activity of the posterior hypophysis which is delicately adjusted to the degree of body hydration. Thus, after the ingestion of water, posterior pituitary activity is diminished, the concentration of antidiuretic hormone in the blood falls, tubular reabsorption of water decreases and diuresis results. On the other hand, some workers postulate the existence of a specific diuretic hormone to account for water excretion. One may say with a fair degree of certainty, however, that regardless of the particular hormonal mechanism responsible for diuresis, decreased tubular reabsorption is the basis of water diuresis.

In edematous individuals, obviously water administration cannot be employed as a diuretic measure, because it would further promote the formation of edema fluid.

Sodium Chloride

Sodium chloride is an efficient diuretic. Its ionic composition allows large amounts of isotonic solution to be administered by parenteral routes without seriously changing the composition of the extracellular fluid. The diuretic value of sodium chloride is not to rid the body of edema fluid but to cause a copious urine flow useful in promoting the excretion of toxic products in low concentration.

The diuretic action of sodium chloride solutions is related to the concentration administered. When isotonic solution (0.9 per cent) is given, elimination is slow and prolonged. As the concentration is increased or decreased, however, the rate of urine formation is more markedly affected. The intensity of the diuresis is related to the degree of distortion in the electrolyte concentration of the body fluids (Figure 66).

Mechanism of Diuretic Action. The administration of *isotonic sodium chloride solution* increases the volume of extracellular fluid, and therefore the circulatory volume, to a much greater extent than does an equal amount of water.

Water distributes itself throughout the fluid media of the body, *i.e.*, cells and extracellular fluid, which together comprise 70 per cent of the body weight. Isotonic sodium chloride solutions, in contrast, remain in the extracellular fluid reservoir which forms 20 to 25 per cent of the body weight. This selective distribution results from the impermeability of cell membranes to the sodium (Na^+) ion. The osmotic pressure of the sodium retained in the extracellular fluid prevents any passage of water into the cell. (*See* the pharmacology of ions, page 580.) Thus, after the administration of large amounts of isotonic sodium chloride solution, blood volume is increased and the concentration of serum protein is decreased. These changes promote a more copious glomerular filtration, and hence diuresis results. The administration of isotonic sodium chloride solution does little to alter tubular activity. No changes in the fluid content of the body cells have occurred. The concentration of total electrolyte which is regulated so accurately by the kidney is unchanged. The slow and sustained diuresis is therefore mainly the result of increased glomerular filtration (Figure 66).

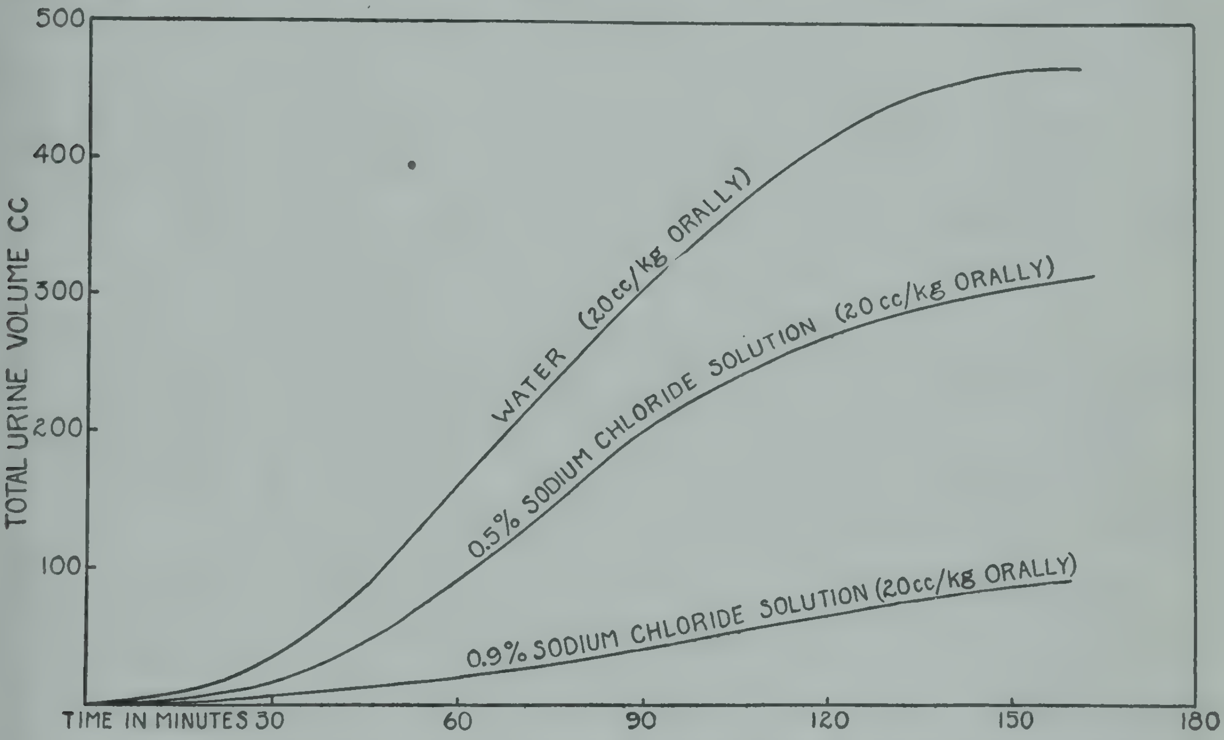


FIGURE 66. *The diuretic action of water and sodium chloride solutions given orally to an unanesthetized dog.*

Administration by stomach tube at 0 time. Water distorts the composition of all the body fluids. It is therefore rapidly excreted by mechanisms discussed in the text. The administration of 0.9% solution of sodium chloride raises only the extracellular fluid volume and changes the chemical composition of this fluid but little. The slight diuresis which results is probably due mainly to an increased rate of glomerular filtration. The 0.5% solution of sodium chloride causes an intensity of diuretic action intermediate between that of isotonic sodium chloride solution and water.

Following the injection of *hypertonic sodium chloride solutions,* the extracellular fluid reservoir is increased not only by the volume of the injection but also by the water withdrawn from the cells to maintain osmotic equilibrium between intra- and extracellular fluids. Blood volume is again increased, serum protein concentration decreased, and glomerular filtration enhanced. In addition, the increase in the electrolyte concentration of the body fluids leads to a decreased reabsorption of sodium chloride by the tubules. The osmotic effect of this rejected sodium chloride in the tubules limits reabsorption of water. The highest concentration which sodium chloride can reach in the urine of man approaches two per cent. Therefore, with the rejection of every gram of sodium chloride by the tubules there is an obligatory water excretion of about 50 cc. Thus diuresis from hypertonic sodium chloride solutions is the result both of increased glomerular filtration and decreased tubular reabsorption, and is greater than that obtained from isotonic solutions.

In clinical edema, the use of sodium chloride as a diuretic is to be avoided, because this electrolyte can enhance the formation of extracellular fluid.

Potassium Salts

Potassium salts, in contrast to those of sodium, are effective diuretics in any concentration. The two commonly employed salts of potassium are the chloride and the nitrate, but the bicarbonate, acetate and citrate have also been used (Keith and Binger, 1935). The three diuretic salts last mentioned, in addition, will render the blood and urine more alkaline, and are particularly valuable when it is also desirable to combat or prevent acidosis.

Mechanism of Diuretic Action. Potassium is the main cation of the cells of the body. When present in the extracellular fluid, it is filtered through the glomerulus and rejected by the tubule. Inasmuch as there is a well-defined limit in the degree to which the renal tubule can concentrate electrolytes, the excretion of potassium must be accompanied by appreciable amounts of water.

Toxicity. In employing potassium as a diuretic, one must take cognizance of the toxic properties of this ion. In high concentration, potassium is depressant to cardiac muscle, voluntary muscle and nerve (page 596). Toxic manifestations may result especially when potassium salts are administered to an individual with impaired renal function. If kidney function is normal, the ion is excreted so rapidly that little change in the blood level of potassium is noted.

Therapeutic Uses. Potassium gives best results in cardiac edema, although it may be used in edema due to other causes. It is often more effective when combined with a diet low in sodium chloride, potassium chloride rather than sodium chloride being used to flavor the food. The usual dose of a potassium salt is five to 10 grams daily, given orally in divided portions at meal time in 0.5 gm capsules or tablets, enteric coated to lessen gastric irritation. Like many diuretics, potassium salts often fail to produce results. (*See* page 598 for preparations.)

Acid-producing Salts

Salts which tend to produce acidosis are powerful diuretics. Their action is greater than would be expected from their "osmotic effect" and one is obliged to consider their acid-forming properties in explaining the mechanism of the diuresis they produce. The most widely used of the so-called acidifying diuretics are *ammonium chloride, ammonium nitrate* and *calcium chloride.* The ammonium salts owe their acid-forming properties to the fact that the ammonium (NH_4^+) ion is converted in the body to urea, leaving the chloride or nitrate (Cl^- or NO_3^-) ion free to combine with available cation, which is liberated from the elastic bicarbonate (HCO_3^-) ion. The large reduction in bicarbonate alters the $BHCO_3$:H_2CO_3 ratio to such an extent that acidosis results. The administration of calcium chloride also leads to the same end-result. In this instance, the excretion of calcium (Ca^{++}) into the intestine or its deposition in bone allows the chloride ion to displace bicarbonate in the extracellular fluids.

The acid-forming diuretics have been extensively studied by Gamble and associates (1925) and by Keith and Whelan (1926). Following their administration, in addition to the chemical changes in the blood already described, there is an increase in the excretion of fixed base in the urine. This excretion of base is accompanied by water so that the concentration of base in the body fluids remains unchanged. In the presence of edema, most of this base comes from the extracellular fluid, and diuresis may be marked.

Mechanism of Diuretic Action. There are two possible explanations for the diuresis. The first has to do with that function of the kidney which helps to maintain a constant composition of body fluids. When confronted with an excess of anions the kidney will favor their excretion by diminished tubular reabsorption. According to this explanation, the water loss represents an osmotic obligation due to the excretion of unusual amounts of salts.

The alternative hypothesis considers the water loss to be primary and the excretion of salts merely a defense mechanism of the body to maintain a constant osmotic pressure in the face of a large fluid loss. Gamble and associates (1925) favor the latter view, and consider the acidosis to be the basic mechanism of the primary water diuresis. In the face of increased body acidity, the base-binding capacity of the proteins is so altered as to affect the Donnan equilibrium, upsetting the osmotic adjustments between the several compartments of body water and favoring a movement of fluid toward the kidney. Salt is then excreted in order to maintain the composition of the body fluids.

An additional interesting feature of the acid-forming salts is their ability to potentiate the action of mercurial diuretics, for which purpose they are frequently employed. This property is discussed under the mercurial diuretics.

Therapeutic Uses. The preparations employed in therapy are described elsewhere (calcium chloride, page 603; ammonium chloride and nitrate, page 610). The acid-forming saline diuretics are given orally. They may cause gastric irritation and are likely to induce nausea and vomiting. Ammonium nitrate produces the least gastro-intestinal distress, but occasionally it may give rise to methemoglobinemia. The most convenient method of administering all these salts is in enteric-coated tablets or capsules, given in amounts of from eight to 12 grams daily, in divided doses at meal time. In many instances, the salts must be given for several days in order to produce the desired effects. They should not be employed when renal function is markedly impaired, as in chronic nephritis, because of the real danger of producing uncompensated acidosis.

Urea

In addition to salts (electrolytes), certain *molecules* may also be used effectively as diuretics. Of these, urea is by far the most important.

Mechanism of Diuretic Action. Normally, about 50 to 60 per cent of the urea filtered through the glomerulus escapes reabsorption. There is a limit to the concentration which urea as well as electrolyte can attain in the lumen of the renal tubules. Therefore, attending the excretion of urea there is an obligatory loss of water from the body because of the osmotic activity of the unabsorbed fraction. Inasmuch as urea can be administered in large amounts, this water loss may be appreciable.

Preparations. *Urea,* N.N.R., CO $(NH_2)_2$, consists of colorless, odorless crystals freely soluble in water to form a solution having a cooling saline taste.

Therapeutic Uses. Successful results with urea as a diuretic have been obtained in cases of long-standing cardiac edema, chronic nephrosis, and the nephrotic type of glomerulonephritis. Urea is contraindicated when the renal function is markedly impaired, but mild elevations of non-protein nitrogen of the blood do not preclude its use. Urea may be given in fruit juices, iced fluids, or syrup of acacia to mask its taste. The usual single dose is 20 grams, taken two to five times daily.

Glucose and Sucrose

In addition to urea, other molecules are sometimes used as diuretics. The two most commonly employed are glucose and sucrose.

Mechanism of Diuretic Action. Glucose, in order to prove effective as a diuretic, must be given in sufficient amount to exceed the renal threshold for this substance. The glucose which escapes reabsorption in the proximal tubule of the kidney exerts an osmotic effect in the loop of Henle and thus brings about the excretion of water. Inasmuch as considerable glucose may be deposited as glycogen in the liver, one has to effect a sudden change in the glucose concentration of the blood in order to deflect appreciable amounts through the kidney. Consequently, the oral administration of glucose with the attending slow and even rate of intestinal absorption is not an effective diuretic procedure. Glucose must therefore be given intravenously in large doses and in high concentration. The usual dose is 50 cc of a 50 per cent solution.

In several respects, sucrose is a more efficient diuretic than glucose. Although the sucrose molecule is twice as large as the glucose molecule, and therefore exerts only one-half the osmotic effect of glucose gram for gram, nevertheless it possesses two desirable features. When sucrose is administered intravenously, it cannot be metabolized by the body and circulates as a foreign substance until excreted by the kidney. Also, the kidney treats sucrose as a foreign substance and its tubular reabsorption is negligible when compared with that of glucose. Consequently its diuretic action is more certain and more lasting. Obviously, the route of administration must be intravenous for orally administered sucrose would merely be absorbed from the intestine as glucose and levulose. The usual dose is 100 cc of a 50 per cent solution.

Toxicity. Although solutions of hypertonic glucose can be injected with little fear of toxicity, evidence is accumulating that the intravenous administration of sucrose in hypertonic solution is not the benign procedure it was once believed to be. Helmholtz (1933) pointed out that the injection of a hypertonic solution of sucrose in rabbits resulted in renal changes. This observation was confirmed in dogs by Lindberg and his associates (1939). That renal damage from sucrose can occur in human beings was convincingly demonstrated by Anderson and Bethea (1940). They noted, in the course of routine autopsies, a peculiar type of renal lesion which they recognized as being similar to that described in the experimental studies already cited. In every instance they could account for the lesion on the basis of the patient having received a hypertonic solution of sucrose intravenously.

The renal lesion produced by sucrose is characterized by extreme foamy swelling of the lining cells of the renal convoluted tubules of such a degree that the lumen may be invisible. The change may progress to death of the cells. Characteristic tubular lesions may be well developed three hours after the administration of sucrose. The glomeruli are also affected, but to a lesser degree (Anderson and Bethea, 1940). Despite the fact that Lindberg and associates (1939) have demonstrated by the use of renal function tests that the injection of a single dose of 200 cc of a 50 per cent sucrose solution does not impair renal function in normal human subjects or further diminish it in patients with pre-existing renal impairment, nevertheless Anderson and Bethea (1940) recommend, on the basis of their pathological findings, that sucrose should not be injected into patients with renal lesions, and in no instance should large or repeated doses be given.

Therapeutic Uses. Hypertonic solutions of sucrose and glucose are effective osmotic diuretics. In addition they dehydrate tissues and attract water into the blood stream when given intravenously. They are thus used in the treatment of cerebral edema, shock, and circulatory collapse. *Glucose* and *Sucrose* are official in the U.S.P. and B.P., and are marketed in sterile aqueous solution in ampules in varying concentrations up to 50 per cent.

Acacia

Edema caused by low concentrations of serum protein, as in nephrosis, malnutrition, chronic diarrheas, etc., should be treated by raising the concentration of serum protein to its normal value. Thus patients with hypoproteinemic edema are treated with high protein diets in order to enhance serum protein formation. Blood transfusions or the administration of concentrated serum also prove helpful in an emergency in the restoration of serum proteins. When one considers, however, that 20 to 30 grams of serum protein may be excreted daily by a nephrotic individual, it is clear that transfusion therapy cannot replace this loss. Occasionally, however, a patient appears to be permanently benefited by transfusion of plasma protein.

Mechanism of Diuretic Action. Intravenous acacia as an agent to restore normal colloidal osmotic pressure has been used successfully in the treatment of nephrotic edema. Acacia is a substance of high molecular weight and does not freely permeate the capillary wall. Its colloidal osmotic pressure is approximately the same as serum protein (*i.e.,* six per cent acacia, 246 to 260 mm H_2O; human sera, 276 mm H_2O) (Saslow, 1939). As long as it remains in the blood stream, acacia will attract fluid and thus enhance mobilization and excretion of edema deposits. The duration of its sojourn in the blood is limited, however, and about 60 per cent is removed within seven days. Furthermore, after the injection of acacia, the colloidal osmotic pressure of the serum falls more rapidly than does the concentration of acacia. This suggests that the smaller more osmotically active particles of acacia are rapidly lost from the circulation (Butt and coworkers, 1939). The residual acacia persists in the blood for long periods, however, and may depress the formation of serum protein (Jackson and Frayser, 1939). When the acacia content of the blood is maintained by repeated administration, acacia may prove to be a remarkable substitute for serum proteins. Dogs whose serum protein has been reduced by repeated plasmapheresis to a level of 0.05 per cent have been kept edema-free by the judicious administration of acacia (Amberson, 1937).

From a purely theoretical consideration, the conclusion must be drawn that acacia acts as a diuretic by substituting for serum protein and thus mobilizing edema fluid. However, when gum acacia is given to normal dogs, there is no increase in creatinine clearance. This indicates that glomerular filtration is not enhanced. The excretion of chloride, nevertheless, is markedly increased, and in the face of a constant rate of glomerular filtration this indicates a tubular site of action of acacia (Goudsmit and coworkers, 1939).

Untoward Reactions. The acceptance of acacia as a diuretic agent was delayed for several reasons. Untoward reactions due to impurities accompanied its early use. When first introduced, a large single dose (one gram per kg in 15 per cent solution) was recommended. The administration of acacia in this manner led to several undesirable side-effects. A precipitous increase in blood volume with a dangerous rise in blood pressure was not uncommon. Certain individuals exhibited alarming anaphylactoid symptoms and headache and vomiting were frequent. Also there is a great tendency for acacia to escape from the circulation when its concentration in the serum is high as a result of large doses. Just as acacia within the capillaries attracts fluid into the circulation and thus promotes its excretion into the urine, acacia in the extracellular tissue spaces tends to fix fluid at that locus. Desposition of acacia in the liver also occurs after injections of large quantities. It has been demonstrated that such a deposition may untowardly affect liver function as evidenced by a decreased galactose and glucose tolerance (Hall, 1938).

Therapeutic Uses and Technic of Administration. Fortunately, careful studies have revealed that acacia may be effective if given daily in sustained courses in proper doses. The routine of treatment as recommended by Landis (1937) is as follows: Six per cent acacia in 0.9 per cent sodium chloride solution is employed intravenously. The patient is first given a skin test to ascertain unusual sensitivity. This is followed by an intravenous test dose of five to 10 grams. If no untoward reactions are manifest, a course consisting of 20 to 30 grams daily for six to nine days (total of 120 to 180 grams) is instituted. The intravenous injections should be made slowly and only clear solutions used. Prior medication with amytal or morphine has been found to decrease uncomfortable side-effects.

Goudsmit and Binger (1940) recommend a somewhat similar routine. They employ a six per cent solution of acacia in 0.06 per cent sodium chloride. Potassium nitrate is administered for two days before the course of acacia is begun. A course consists of three or four injections of 500 cc of the solution described, given daily or on alternate days. One hour should be taken for the injection. The following untoward reactions have been observed: In 10 per cent of cases an urticarial reaction may occur which can be controlled readily with epinephrine and which does not preclude subsequent injections. Occasionally, during or shortly after an injection, a patient may complain of dyspnea or pain in the left side of the thorax. The injection should be stopped and codeine (30 to 60 mgm) may be administered. Fever of three to four hours duration may follow an injection, but this reaction is observed less frequently than after the transfusion of blood. Goudsmit and Binger do not believe that there is any valid contraindication to the use of acacia except in the very rare case in which a severe allergic reaction to it has occurred. They have failed to observe any untoward effect on blood pressure or on renal or hepatic function and have even administered acacia in cases of severe hepatic cirrhosis without inducing further damage.

Following courses of acacia, weight reductions of 11 kilograms from the loss of edema fluid have been reported. Significant diuresis may ensue on the third or fourth day of acacia therapy. The chances for favorable results are enhanced by a rigid dietary restriction of sodium chloride. Acacia therapy is purely symptomatic and only of temporary value because, following the ultimate excretion of acacia, edema fluid will once more accumulate unless the underlying pathological condition has improved.

Even when no diuresis results from the administration of acacia, beneficial effects may still have occurred, as demonstrated by the subsequent response to

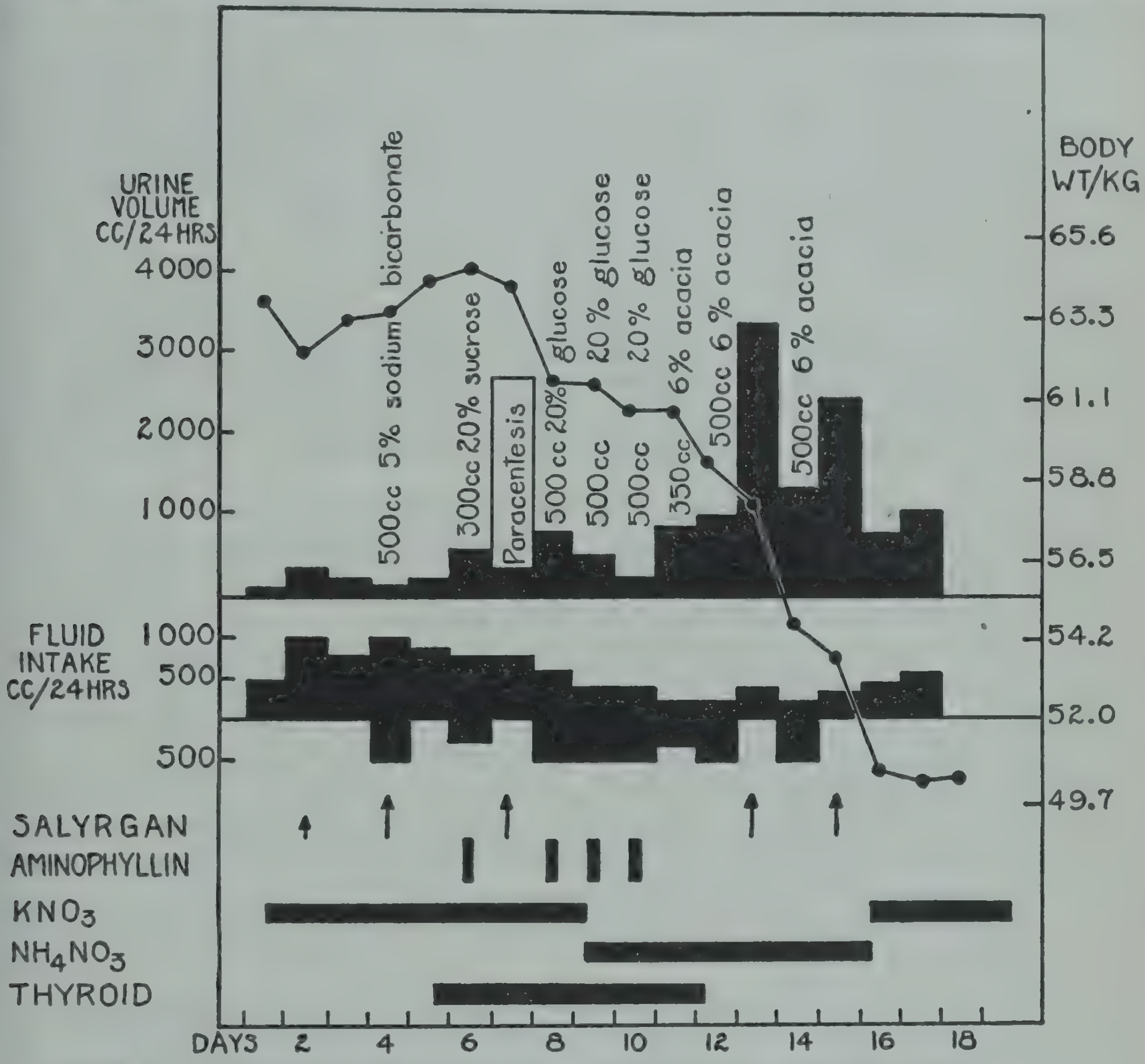


FIGURE 67. *The use of acacia in the treatment of refractory nephrotic edema.*

Upper black blocks, volume of urine per 24 hours; lower black blocks, intake of fluid per 24 hours (above zero line, intake by mouth; below zero line, intravenously); weight curve is shown in solid black line. *Medication:* salyrgan, full-size arrow represents 2 cc given intravenously, smaller arrow 1 cc; aminophyllin, 0.24 gram mixed with other solutions given intravenously; potassium nitrate or ammonium nitrate, 9 grams per day by mouth; desiccated thyroid, 0.6 gram per day by mouth.

Female, aged 27, nephrotic edema of several months standing. Laboratory findings: 24 hour urine output of 150 cc; specific gravity 1.043; albumin four plus; serum protein 4.4 grams per cent; albumin-globulin ratio of 1:5; calculated colloidal osmotic pressure of the serum was less than 40 per cent of normal. The patient proved refractory to treatment consisting of a combination of the following measures: restricted fluid intake, high protein-low salt diet, and the drugs depicted in the chart. The weight loss occurring on the seventh day represents the fluid removed by paracentesis. Satisfactory diuresis was not obtained until acacia was administered. Following acacia therapy, the patient also became responsive to salyrgan. Note the varied therapeutic attack and that acacia was not used until all other medication failed. (After Goudsmit and Binger, 1937. Courtesy of the Division of Publications, Mayo Clinic.)

other diuretics. It has been shown that patients previously refractory to all diuretics will lose this refractory state following a course of acacia, despite the fact that there was no striking diuretic response to the acacia itself (Figure 67)..

At present acacia is used conservatively. It is reserved for cases of persistent, severe nephrotic edema that have resisted other forms of therapy and may provide symptomatic relief unobtainable by other procedures. Furthermore, the edema-free state renders the patient with nephrosis less susceptible to streptococcal and pneumococcal infections to which he may otherwise succumb.

Preparations. Acacia is available in ampules containing 100 cc of a sterile 30 per cent solution, either in distilled water or with 4.5 per cent sodium chloride. In nephrotic patients, the salt-free solution is best employed. The content of the ampules is diluted with four volumes of sterile distilled water before injection. The acacia-sodium chloride solution is used in shock therapy.

Xanthines

The xanthines—caffeine, theobromine and theophylline—in addition to their pharmacological properties considered elsewhere (page 275), have a pronounced diuretic action. This activity, coupled with the absence of toxic effects, has led to the wide use of these compounds as diuretic agents.

Mechanism of Diuretic Action. The controversial subject of the mechanism of action of the xanthine diuretics has been extensively investigated. Von Schroeder (1887) believed that caffeine stimulated the secretory activity of the renal tubule. As the vitalistic theory of renal function gave way to the modern theory, the action of the xanthines on the renal circulation received more attention. The rate of urine flow was correlated with increase in renal volume. Sollmann and Pilcher (1912) demonstrated that caffeine caused marked dilatation of renal vessels previously constricted by epinephrine. Apparently convincing evidence of the vascular mechanism of xanthine diuresis was offered by Richards and Schmidt (1924) when they demonstrated that in the frog, after the administration of caffeine, the number of functioning glomeruli was increased. In fact this observation has led to the concept that normally all the glomeruli of the kidney are not functioning at the same time, but the number may vary according to the excretory demands.

All the experimental evidence, however, is not in complete support of the vascular site of xanthine action. For example, Cushny and Lambie (1921) observed that the diuretic action of caffeine far outlasted the vasodilatation of the renal vessels. In an attempt to explain this discrepancy, they postulated that the permeability of the glomerular capsule must be increased and thus glomerular filtration enhanced. Still other mechanisms of action have been postulated. It has been claimed that the affinity of serum proteins for water is reduced, and evidence has also been presented to show a mobilization of fluid into the blood under the influence of these drugs. These two phenomena would enhance glomerular filtration.

Renal Clearance Technic. When caffeine diuresis is investigated by means of the renal clearance test, an entirely new concept of xanthine action is revealed and demands consideration.

The clearance technic was introduced by Rehberg (1926) and has become an important tool in the hands of renal physiologists. It is simple in principle. If a substance is filtered through the glomerular capsule, completely rejected by the tubule, and not secreted by the tubular epithelium, the ratio of the concentrations of this substance in blood and urine becomes a measure of tubular reabsorption of water. Furthermore, the total amount of the substance found in the urine over a given period of time divided by the average of its blood concentration during the collection period is a measure of the amount of glomerular filtrate formed during that period.

An example of the type of data obtainable will clarify this procedure. The two compounds most extensively used in clearance technics are inulin and creatinine. Assume that an individual received inulin in sufficient amount to bring the blood level of this foreign polysaccharide to 100 mgm per cent; that 50 cc of urine were excreted over the observation period of 30 minutes; and that the concentration of inulin in this urine was found to be 7.5 per cent (7500 mgm per cent). The kidney concentrated the inulin from the level of 100 mgm per cent found in the blood, and therefore in the glomerular filtrate, to the level of 7500 mgm per cent found in the urine. Since there is ample experimental evidence to show that the renal tubules neither reabsorb nor secrete inulin, the mechanism of this renal concentration must have been through the tubular reabsorption of water. The tubules concentrated the inulin of the glomerular filtrate 75 times. Therefore one cc of urine was formed from every 75 cc of glomerular filtrate and the tubules reabsorbed 74 of every 75 cc or 98.7 per cent of the fluid passing through them. Over the 30 minute period, 3750 milligrams of inulin were recovered in the urine (50 cc urine × 75 mgm per cc). The concentration of diffusible substances in the glomerular fluid is known to be the same as that in the blood. Inasmuch as the concentration of blood inulin over the observation period was 100 mgm per cent, 100 cc of glomerular filtrate were necessary to supply the urine with 100 mgm of inulin. Therefore the 3750 mgm of urine inulin must have been derived from 3750 cc of glomerular filtrate. This represents a glomerular filtration rate of $\frac{3750}{30}$ or 125 cc per minute, which is normal for an adult.

The clearance technic has been described because it has afforded so much information on the site of action of diuretic drugs. If the *total amount* of inulin in the urine does not increase during a period of diuresis, it is obvious that the rate of glomerular filtration has not been altered. It also follows that any decrease in the *concentration* of inulin in the urine represents decreased activity on the part of the tubules in the reabsorption of water. Walker and coworkers (1937) made a careful study of xanthine diuresis in dogs and rabbits, utilizing the clearance technic combined with measurements of renal blood flow. They concluded that in xanthine diuresis the rate of renal blood flow and glomerular filtration are not significantly affected, and that xanthine diuresis results from decreased tubular reabsorption of fluid. A quantitative experiment of this type does much completely to negate earlier conclusions as to the mechanism and site of xanthine diuresis. Similar data have been obtained on man by Blumgart and associates (1934).

Preparations and Doses. The xanthines are not equally potent as diuretics. Theophylline has the strongest action; theobromine is slightly less potent; and caffeine is definitely the weakest. Theobromine, however, gives a more sustained action than theophylline. Caffeine is not employed as a diuretic because of its weak action and also because of its stimulation of the central nervous system. This latter undesirable side-effect is not evident with theophylline or theobromine.

An advantage of the xanthine diuretics is that they are active after oral administration. A number of theobromine and theophylline preparations are available. *Theobromine,* N.N.R., may be used in a dose of 0.6 gram, three to five times daily for several days. When its salts are employed, the lower theobromine content necessitates raising the dose to one gram, three to five times daily. The salts available are *Theobromine with Sodium Salicylate,* U.S.P. (Diuretin), *Theobromine Sodium-Acetate* (Agurin), N.N.R., and *Theocalcin* (calcium theobromine and calcium salicylate), N.N.R. All the theobromine preparations are capable of producing gastric distress, nausea and vomiting. Theobromine itself and theocalcin are somewhat less troublesome in this respect. *Theophylline,* U.S.P., B.P., may be given in a dose of 0.3 gram, three to five times daily for several days. The more commonly used salts are *Theophylline with Sodium Acetate,* U.S.P., *Theophylline Calcium Salicylate,* and *Theophylline Ethylene Diamine* (Aminophylline), U.S.P., and the dose of any of these is 0.5 gram, three to five times daily. Here again, a major side-action is gastric irritation. (For details of preparations, *see* page 281.)

Therapeutic Uses. The xanthines cause little diuresis in the absence of edema. They are also ineffective when renal function is impaired by glomerulonephritis, renal arteriolosclerosis or other causes, and are not very useful in nephrotic edema. Best results are obtained in cardiac edema when renal function is good (Figure 68). Tolerance to their diuretic action is developed in a few days, but a short rest period usually restores susceptibility. Although the xanthines are less powerful and less certain in action than the mercurial diuretics,

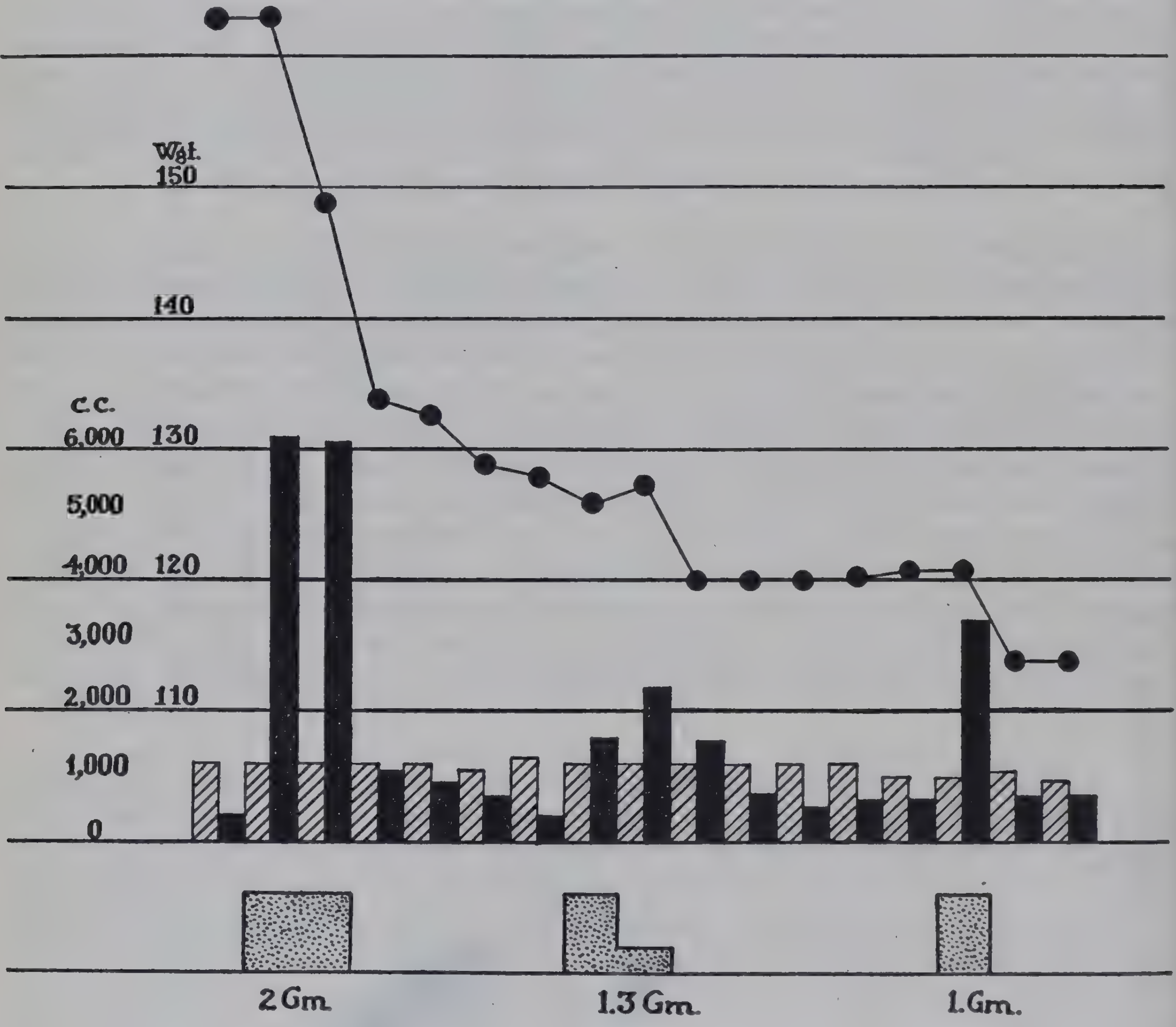


FIGURE 68. *The diuretic response to theophylline.*

Female, aged 62, with arteriosclerotic hypertensive heart disease and auricular fibrillation. Blood pressure, 230/120. Complete digitalization and rest for eight days caused no diminution in the extensive edema. Theophylline was given orally on three separate occasions (0.3 gram three times daily) and caused great diuresis, with loss of 30, 8, and 7½ pounds, respectively. The daily fluid intake is indicated by cross-hatched columns, the daily urinary volume by solid columns, weight in pounds by dots and theophylline by stippled rectangles. The desired amount of theophylline could not be given at its second and third administration because of nausea and vomiting. Digitalis was given only in maintenance doses, an average of one gram per week. (After Marvin, 1926. Courtesy of *The Journal of the American Medical Association.*)

low toxicity is a strong point in their favor. Even after excessive doses, they cause no structural damage to normal renal tissue.

Mercurials

The mercurial diuretics have the justified reputation of being the most powerful and consistently effective of all diuretic drugs. Calomel (mercurous chloride) was used as a diuretic by Paracelsus in the sixteenth century. It was an ingredient of the famous "Guy's Hospital pill" (calomel, squills and digitalis), and contributed greatly to the diuretic action of this combination of drugs. Despite its efficacy, calomel has been largely displaced by the organic mercurials, mainly due to its drastic cathartic effect and uncertainty of intestinal absorption.

Merbaphen (Novasurol) was originally introduced as an antisyphilitic agent and contains mercury in complex organic combination. Although it was a poor therapeutic agent against syphilis, its potent diuretic properties were soon discovered (Saxl and Heilig, 1920), and it is now used exclusively for its renal action. The value of merbaphen as a diuretic led to the introduction of *Salyrgan* (Mersalyl) in 1924. Salyrgan was found to be equal to merbaphen in activity but much less toxic and consequently it is now more widely employed. Subsequently introduced organic mercurial diuretics are *Mercupurin* and *Mercurin*. Mercupurin is distinctive in that it contains theophylline. It is doubtful, however, whether the theophylline adds significantly to the predominant diuretic action of the mercury. The xanthine, however, may facilitate the absorption of the diuretic mercurial. Present indications suggest that mercupurin and mercurin are on a par with salyrgan with respect to diuretic activity and toxicity.

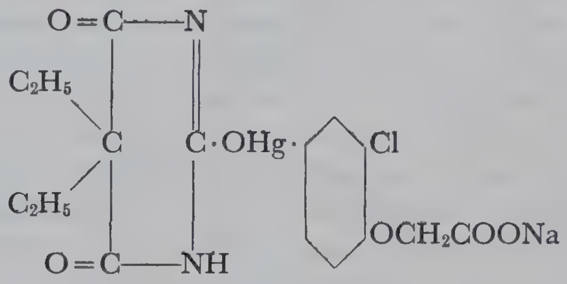
Mechanism of Diuretic Action. The pharmacological actions of and therapeutic indications for all the organic mercurials are so similar that these drugs are conveniently discussed as a group. As in the case of the xanthines, there is no unanimity of opinion as to the mechanism of action. Some consider the site of action of mercurial compounds to be extrarenal. For example, it has been claimed that the "water-binding" power of the serum proteins is reduced by mercury. Evidence has also been advanced that there is a reduced concentration of hemoglobin and protein in the blood and an increased volume of circulatory fluid following the administration of mercurial diuretics. This fluid is presumably mobilized from the liver.

More convincing, however, is the evidence favoring a direct renal action. The experiments of Govaerts (1928) have been widely cited in this regard. At the height of novasurol diuresis, Govaerts transplanted the kidney from a mercurialized dog to the neck of a normal dog. The transplanted kidney continued to exhibit a diuresis whereas the control kidneys of the host excreted urine at a much lower rate. Confirmatory evidence was then obtained by experiments which were the exact counterpart. When a normal kidney was transplanted into the neck of a mercurialized animal, the organ failed to show any diuresis when the host's kidneys were secreting at an enhanced rate. Govaerts' results thus prove conclusively that extrarenal factors are not necessarily involved in mercurial diuresis. As still further proof of a direct renal action, Bartram (1932) showed that when a small dose of mercurial diuretic is slowly injected directly into a renal artery of one kidney, that kidney responds with a diuresis while the opposite kidney continues to form urine at its normal rate. Lastly, renal clearance experiments in dogs show that salyrgan causes diuresis despite a constant blood flow and an unchanging rate of glomerular filtration (Walker and associates, 1937).

The necessary interpretation is that these diuretic agents act by reducing tubular reabsorption of water. Similar results have been obtained in man (Blumgart and coworkers, 1934).

The action of the organic mercurial diuretics on renal tubules represents a very early stage of the toxic action of mercury on the kidney (page 733). The mercuric ion (Hg^{++}) released from the organic mercurials probably accounts for the renal effects. Sollmann, Schreiber, and Cole (1936) demonstrated that ionizable inorganic compounds of mercury are more potent in diuretic action than the non-ionized organic mercurials. Although no histological evidence of renal damage follows the therapeutic use of organic mercurial diuretics, nevertheless precautions should be taken to prevent cumulative toxic effects, and injections of these compounds should be spaced at least four days apart.

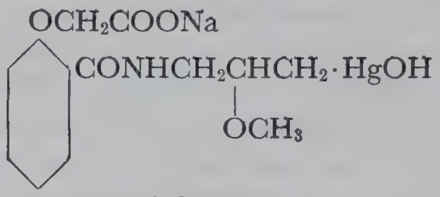
Preparations and Doses. *Merbaphen,* U.S.P., (Novasurol) is a complex organic mercurial containing 34 per cent mercury and having the following structural formula:



Merbaphen

The substance is a white, crystalline, water-soluble powder. It is marketed in ampules containing one cc of a 10 per cent solution. The dose is one to two cc.

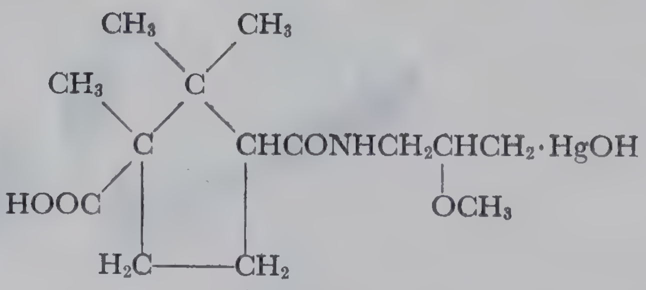
Salyrgan, N.N.R., (*Mersalyl,* B.P.) is a complex organic mercurial containing 39.6 per cent mercury and having the following structural formula:



Salyrgan

It is a white, crystalline, water-soluble powder and is marketed in ampules containing one or two cc of a 10 per cent solution. The dose is one to two cc.

Mercurin, N.N.R., is a complex organic mercurial containing 39 per cent mercury. It is a white, non-crystalline, insoluble powder of the following structure:



Mercurin

Mercurin is marketed in the form of cocoa butter suppositories containing 0.5 gram of the drug. The dose is one suppository by rectal administration.

Mercupurin, N.N.R., is a combination of mercurin and theophylline, the two molecules probably being chemically combined. The substance is marketed in a solution which contains 100 mgm of mercurin (39 mgm of mercury) and 35.3 mgm of theophylline per cc. It is available in ampules containing one or two cc of the aforementioned solution. The presence of the xanthine supposedly results in more rapid and complete absorption of the mercurial if the intramuscular route is employed (De Graff and associates, 1938). If the intravenous route is employed, sloughs and venous thromboses occur with less frequency and severity than following salyrgan or merbaphen.

Salyrgan-Theophylline Solution, N.N.R., (*Injection of Mersalyl,* B.P.), is a solution containing ten per cent of salyrgan and five per cent of theophylline to facilitate absorption. It is marketed in ampules containing one or two cc of solution. The dose is one to two cc.

Salyrgan is also marketed in suppository form, but this product is not included in the N.N.R. due to rectal irritation which the drug produces (Report of the Council, 1939; De Graff and associates, 1939).

Routes of Administration. The route of administration of the mercurial diuretics is intravenous, intramuscular or rectal. Mercurin is used exclusively by the rectal route. The rectal use of organic mercurials is contraindicated in proctitis and other inflammatory diseases of the rectum. It remains to be seen, however, whether the mercurial diuretics at present available can be given rectally with impunity to patients without rectal disorders. For parenteral administration, many clinicians favor the intramuscular over the intravenous route. Intramuscular injection should be made deep in the gluteal muscles. This route has definite advantages, especially in the following respects: (1) intramuscular injections often are effective when intravenous medication fails; (2) it avoids the dangers of tissue slough from extravasation and thrombophlebitis from repeated intravenous injection; (3) there is less danger by this route in patients with badly damaged hearts; (4) chronic intramuscular medication is independent of the availability and patency of veins. The pain which sometimes accompanies intramuscular administration of organic mercurials may be eliminated by the addition of a local anesthetic to the solution. The possiblity of extravasation during intravenous injection can be minimized by the use of a very small needle.

Therapeutic Uses. The main use of the mercurial diuretics is in cardiac edema. Good results are sometimes obtained in chronic nephrosis, the nephrotic type of glomerulonephritis, and ascites due to liver cirrhosis or portal obstruction.

The diuretic response to the mercurials usually starts two to three hours after their administration and ceases after 12 to 24 hours. During this period, 85 per cent of the injected mercury is excreted in the urine. Diuresis is most copious in its early stages, and the drug should therefore be given in the morning in order to allow the patient a restful night uninterrupted by the necessity of urinating. In edematous individuals, as much as 10 liters of urine may be excreted following a single injection. As is true of all diuretics, however, the action of the organic mercurials is variable and at times may fail completely. In some instances, diuresis follows the first administration and subsequent injections then become progressively less effective. The development of tolerance, however, is not the rule, and salyrgan may be used weekly over a period of many years with no diminution in the diuretic response.

Potentiation with Other Diuretics. Although the mercurials are often used alone, especially good results are obtained when they are combined with other diuretics, notably the acid-forming salts. The acidifying salt should be administered in full doses for at least 48 hours prior to the mercurial (Figure 70). The resulting diuresis is often greater than the total of the diuretic responses obtainable from each agent given separately (Figure 69). The mechanism of this potentiation is not understood. Apparently acidosis increases and alkalosis decreases the diuretic response to the mercurials (Ethridge, Myers and Fulton, 1936).

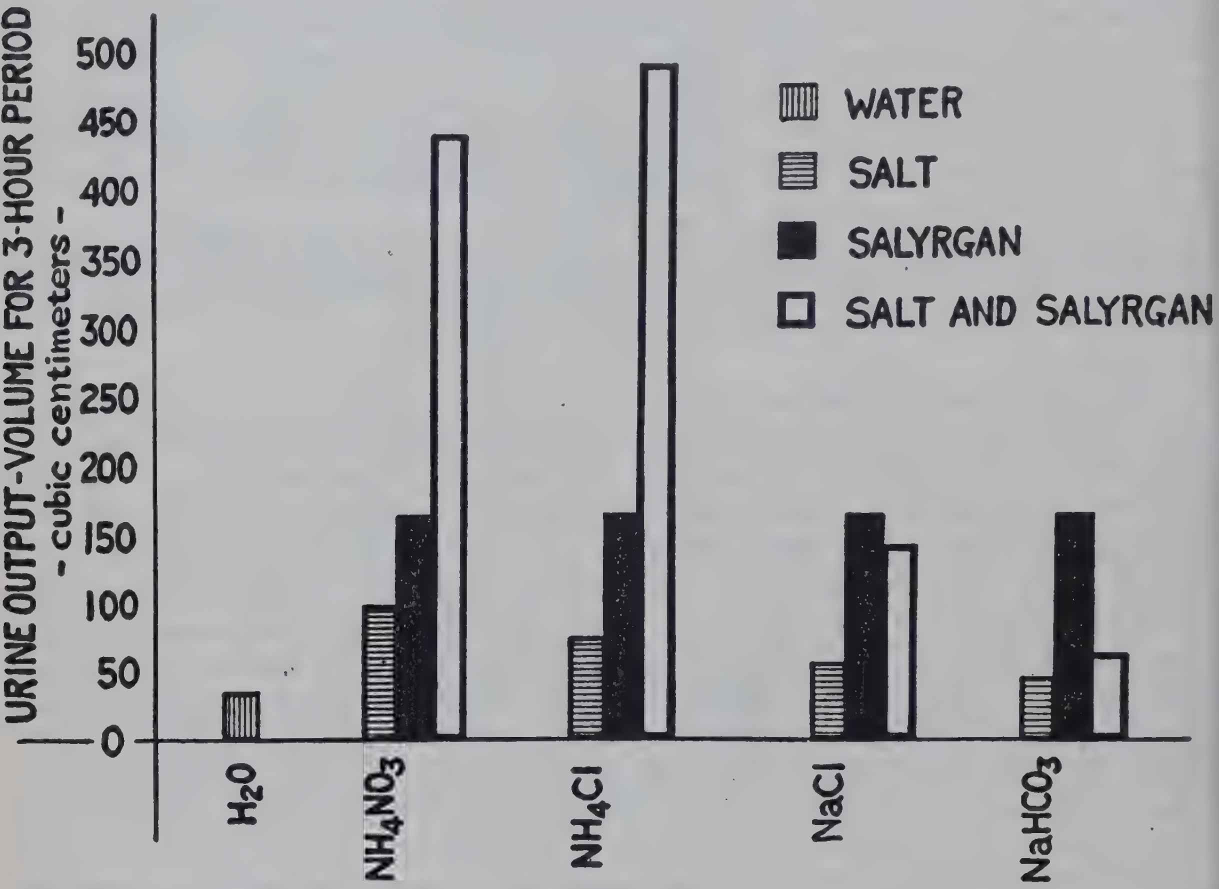


Figure 69. *The effect of acidifying, neutral and alkalinizing salts on the diuresis produced by salyrgan.*

Each result represents an average for the same four dogs. Neutral salts exert no appreciable effect on salyrgan diuresis, whereas alkaline salts inhibit, and acidfying salts markedly potentiate the diuretic response to mercurials. (After Ethridge, Myers and Fulton, 1936. Courtesy of the *Waverly Press.*)

Untoward Reactions. Untoward reactions may occasionally occur following the use of the mercurial diuretics. The outstanding symptoms are those characteristic of inorganic mercury poisoning (page 733), namely, stomatitis, colitis, albuminuria, hematuria, and circulatory collapse. Poisoning may be due to the failure to eliminate the injected mercury promptly or to an unusual sensitivity to mercury. Certain precautions are usually employed to prevent untoward effects. Organic mercurial diuretics should not be given if renal function is noticeably impaired. A test dose of 0.5 cc is injected 24 hours before the full therapeutic dose. The patient is then observed for untoward reactions and the urine is examined carefully. Constipation should be avoided to prevent accumulation of the mercury excreted into the colon.

MISCELLANEOUS DIURETICS

Certain drugs which are not regarded primarily as diuretics are sometimes useful in promoting the excretion of edema fluid. The most important of these is *digitalis.* In many cases of cardiac edema, digitalization alone will cause a copious urine flow. The mechanism of action is purely circulatory and has been fully discussed (page 516).

Desiccated thyroid will often initiate diuresis, especially if edema is associated with a decreased metabolic rate. The thyroid gland apparently is intimately concerned with water metabolism. If animals are completely hypophysectomized, they exhibit a temporary polyuria as contrasted with the permanent polyuria associated with removal of the posterior pituitary alone (page 647). It has been shown by Mahoney and Sheehan (1935) that if such an animal receives thyroid, the polyuria will persist. The mechanism of this action is not known. Nevertheless, desiccated thyroid is sometimes useful in the relief of refractory edema.

The mechanism of action of *parathyroid extract* in the production of diuresis is also obscure. Both experimental animals and edematous patients respond to repeated injections of parathyroid extract with a sustained diuresis. This diuresis is associated with increased urinary excretion of phosphate. Parathyroid extract is not often employed in the treatment of edema but has been successfully used in the edema of nephrosis. The dose is 20 to 60 units daily. The extract should be reserved for use only in edematous individuals refractory to more commonly employed diuretics. The dangers attending the use of this hormone, the precautions necessary, and the technic of administration are given elsewhere (page 1177).

THE CLINICAL USE OF DIURETICS

The Pathological Physiology of Edema Formation. The chief clinical use of diuretics is to promote the excretion of edema fluid. Starling (1896) established the basic facts concerning the mechanism of edema formation. Edema fluid arises from the blood and results from an imbalance of those forces which govern the passage of fluids across the capillary membranes. The capillary membrane is permeable to all the constituents of the blood with the exception of the serum protein, lipids and cellular elements. Of these substances, the serum proteins exert a measurable osmotic pressure, which is approximately 20 mm of mercury. There is a progressive fall in blood pressure along the course of the capillary from the arterial to the venous end. As long as the hydrostatic pressure within the capillary is greater than the osmotic pressure exerted by the serum proteins, fluid passes from the capillary into the extracellular spaces, and this occurs chiefly at the arterial end. Extracellular fluid diffuses back into that portion of the capillary where the hydrostatic pressure is less than the osmotic pressure of the serum protein, and this occurs mainly at the venous end.

Three major factors favor the loss of fluid from the capillaries into the tissue spaces: (1) an increase in the hydrostatic pressure within the capillary, (2) a decrease in the concentration of serum protein, and (3) injury to the capillary membrane increasing its permeability to protein. In this last condition, the protein content of the extracellular fluid is increased. This extracellular protein exerts an oncotic pressure which opposes that of the serum protein, and this favors edema formation. The protein content of extracellular fluid is negligible as a rule, but in some edema fluids, especially those of an inflammatory origin associated with widespread capillary damage, the protein content may reach one or two grams per cent. Edema fluid under these circumstances may stubbornly resist mobilization.

Mechanisms of Clinical Edema. In the dependent edema associated with cardiac decompensation, the increased hydrostatic pressure within the capillaries is the cause of the escape of fluid into the tissues. The capillary hydrostatic pressure increases as the result of increased venous pressure, transmitted from the right heart to the venous end of the capillary. A fundamentally similar mechanism accounts for the ascites associated with portal cirrhosis. On the other hand, nephrotic edema results from the fall in concentration of serum protein which attends the loss of large amounts of protein, mainly albumin, through the renal glomeruli. Finally, the edema associated with acute glomerulonephritis is due to widespread capillary damage allowing for the escape of protein into the extracellular spaces. This type of edema is not primarily renal in origin, and the capillaries of the glomeruli merely manifest the same pathological changes occurring in other capillary beds.

Mechanism of Action of Diuretics in Mobilization of Edema Fluid. The majority of diuretics, with the notable exception of acacia and digitalis, are not specific therapeutic agents directed against the underlying pathological conditions giving rise to the edema. Rather, they act on the kidney in such a manner as to promote the excretion of fluid in excess of the amount which would normally be eliminated. The direct source of this excess fluid excreted by the kidney is the blood. This would result in an anhydremia were it not for the fact that the transient increase in concentration of serum proteins attracts fluid from the extracellular spaces. In the normal individual, the amount of extracellular fluid is limited. In edema, however, it is large, and with such a copious reservoir to supply the circulation it is not surprising that the response of an edematous individual to a diuretic is usually far greater than that of a normal person.

In edema, diuresis often continues after the pharmacological action of the particular diuretic would normally have ceased. Two factors contribute to this fortuitous circumstance. The edema, when due to congestive heart failure, involves the heart and kidneys as well as the other tissues of the body, and thus tends to perpetuate itself by further impairing the circulation and renal function. Following the partial removal of this edema fluid by a diuretic agent, the improved circulation and renal function aid in the excretion of the remainder. Furthermore, once the predominant direction of the flow of fluid has been reversed to normal and the kinetics of diuresis have been initiated, fluid will continue to flow from the tissue spaces into the circulation in a more or less self-perpetuating diuresis. The composition of the blood after the administration of acacia as a diuretic in nephrosis serves to illustrate this latter point. The initial withdrawal of fluid from the edema deposits often leads to a hydremia in which the oncotic pressure of the serum is even lower than before the acacia was given. Despite this fact, the edema fluid continues to move into the circulation and diuresis persists.

Choice and Clinical Use of Diuretics. The one condition which definitely limits the choice of diuretic drugs regardless of the cause of edema is renal insufficiency. Poor renal function contraindicates the use of mercurials, acid-forming salts, potassium salts, and urea. Of the remaining preparations, the xanthines and hypertonic glucose or sucrose solutions sometimes give favorable results. Some clinicians consider the concentrating ability of the kidney as a sufficiently reliable test of renal function to indicate the limitations of diuretic therapy. If the kidney is capable of concentrating urine to a specific gravity of 1.015, it is considered to have retained sufficient function to allow the use of the more toxic diuretics (Fishberg, 1939). The non-protein nitrogen concentration of the blood or other renal function tests may be used, and the formed elements of the urinary sediment should be carefully studied before selecting a diuretic drug.

When renal function is adequate, a wider choice of diuretics is permissible. In cases of *edema associated with cardiac decompensation,* the use of a diuretic is often unnecessary. Rest in bed, digitalization, and fluid restriction result in an adequate disappearance of edema in approximately 50 per cent of cases. If edema persists despite such a therapeutic regimen, it can usually be cleared with any of the diuretic agents (Figures 68 and 70). According to Hayman (1936), the mercurial diuretics have proved most effective in this condition, being successful in 92 per cent of cases. Urea produced a diuresis in 83 per cent and the xanthines in 66 per cent. As has been stated, the combination of acid-producing diuretics and mercurials is very effective. In order to potentiate the diuresis to mercurials, the acid-forming salts should be given in full dosage for at least two days before the mercury (Figure 70). These salts, however, are likely to cause gastric distress, nausea and vomiting. Therefore, it is often a question whether their administration is warranted, since the mercurials themselves are often so effective. Furthermore, the vomiting may possibly lead to a relative alkalosis from a loss of gastric hydrochloric acid, and thus detract from the effectiveness of a mercurial diuretic.

In cases of *acute glomerulonephritis* in which edema occurs, the edema is quite refractory to diuretic therapy due to several reasons. The effectiveness of diuretics is greatly diminished because of the impaired function of the damaged kidney. Secondly, more potent diuretic agents such as the acid-producing salts and mercurials cannot be used because of the danger of uncompensated acidosis or additional insult to the kidney by mercury. In addition, mercury poisoning is a real danger in nephritic patients. Lastly, the edema of acute glomerulonephritis is mainly due to widespread capillary damage which allows the escape of protein

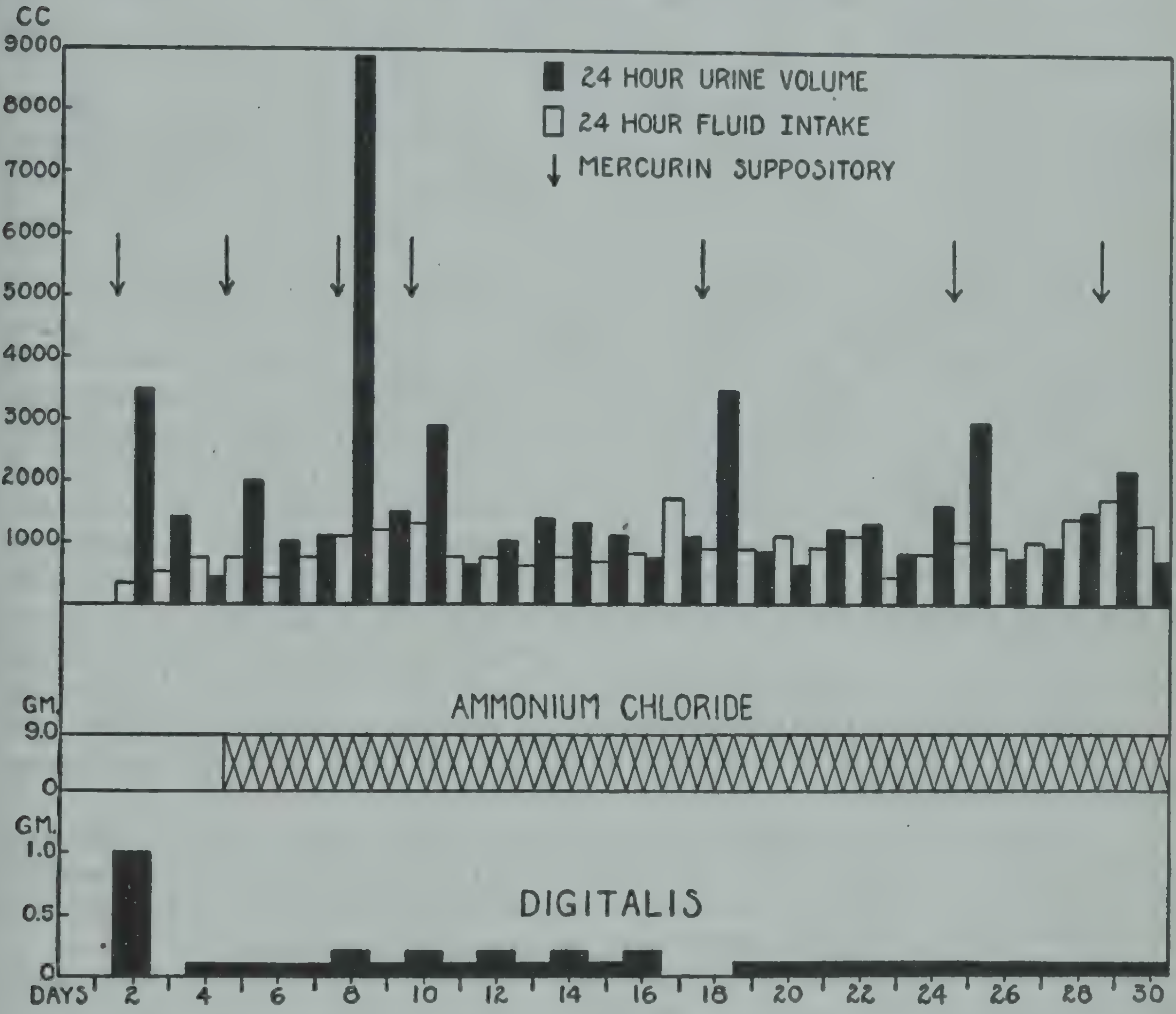


FIGURE 70. *Treatment of the edema of congestive heart failure with mercurial diuretics.*

Female, aged 44, hypertensive cardiovascular disease, congestive heart failure, auricular fibrillation, marked ascites and edema. In response to an increased dose of digitalis, rest in bed and a mercurin suppository, a moderate but unsustained diuresis ensued and marked anasarca, cyanosis and dyspnea persisted. On the fifth day, at which time the patient's condition was more critical than on admission to the hospital, administration of ammonium chloride was started and another mercurin suppository given. The diuretic response was negligible. When mercurin was repeated after four days of ammonium chloride therapy, however, a typical potentiated response was obtained. Mercurin suppositories were given on four subsequent occasions during the next three weeks and in each instance the diuretic response exceeded that of the fifth day when the mercurial was not preceded by an acid-forming salt. This was true despite the fact that the edema was clearing and less fluid was available for excretion. (After Flexner, 1938. Courtesy of the *Annals of Internal Medicine*.)

into the edema fluid and makes the mobilization of the latter most difficult. For these reasons, diuretics are rarely used. Hayman (1936) records 16 cases of acute nephritis in which no response was obtained to diuretic drugs. One relies, therefore, mainly on the proper control of water and electrolyte intake, rather than on drugs designed to hasten fluid output.

On the whole, diuretic agents have limited usefulness in the edema of *subacute or chronic glomerulonephritis.* The choice of diuretic depends mainly on the state of renal function. The xanthines and hypertonic dextrose are occasionally effective. The mercurials cannot safely be used and acid-forming salts must be administered with caution. Fortunately, edema in cases of chronic glomerulonephritis is often transitory and an individual may even run the entire course of the disease without edema. Sometimes edema may attend acute exacerbations of the disease, in which case all the points emphasized concerning the use of diuretics in acute glomerulonephritis would apply.

Edema occurring in *nephrosis,* whether due to renal amyloidosis, chronic lipoid nephrosis, or the nephrotic type of chronic glomerulonephritis, is largely due to the decrease in plasma protein concentration. The response to diuretic agents is difficult to predict. It may be necessary to try several different drugs, alone or in combination. Of the diuretics acting directly on the kidney, the mercurials offer the best chance for success. They may be employed in conjunction with acid-forming salts. They cannot be used, however, unless renal function is relatively unimpaired. Urea, also, is an effective diuretic agent in nephrosis. It may keep patients edema-free over long periods of time, but occasionally it may fail completely. The xanthines are relatively inefficient and even in cases in which they are initially successful, tolerance tends to develop. It is in the refractory cases of nephrotic edema that the use of the less commonly employed diuretics has occasionally met with conspicuous results. For example, parathyroid extract sometimes produces diuresis when other agents have failed. If edema is associated with a low basal metabolic rate, desiccated thyroid will sometimes initiate the excretion of edema fluid. Acacia is also used in treating the resistant edema of nephrosis. If it fails, combination therapy of acacia and a xanthine or mercurial may yield the desired result. Regardless of the diuretic procedure employed, dietary restriction of sodium chloride and a high protein intake are important factors to observe (Figure 67).

The chronic ascites associated with *cirrhosis of the liver, chronic adherent pericarditis,* etc., is often benefited by the use of diuretics. It is usually impossible to prevent completely the accumulation of ascitic fluid exclusively by drugs, but the intervals between paracenteses may be appreciably prolonged by the use of diuretics. The mercurials, given as a rule at weekly intervals, have been most effective. Noth (1937) reports a remarkable case of Pick's disease with chronic ascites treated successfully for more than seven years with 450 doses of mercurial diuretics given intravenously and intramuscularly. During the last three years of this therapeutic marathon, six grams of ammonium nitrate daily were given in conjunction with the mercury. Urea may also be used to diminish the rate of formation of ascitic fluid.

Other Measures in the Treatment of Edema. One is not limited to the use of diuretic drugs in the treatment of edemas. The other procedures available are: (1) the restriction of salt and water intake and the use of high protein diets; (2) the promotion of extrarenal water loss through the skin by sweating and through the gastro-intestinal tract by the use of saline cathartics in hypertonic solution; and (3) the mechanical removal or drainage of fluid from the body cavities or tissues. Any of these procedures may be combined with the use of diuretic agents.

ANTIDIURETICS

Posterior Pituitary

The only antidiuretic substance of practical importance is the antidiuretic principle of the posterior pituitary. A discussion of the active principles of the posterior hypophysis is given on page 661. The antidiuretic principle is one of three pharmacological agents which have been isolated from this part of the pituitary gland. Chemically it cannot be separated from the pressor principle. There is a great deal of evidence, however, which establishes the antidiuretic substance as a true hormone but the hormonal nature of the pressor principle of the pituitary has not been proved.

Physiological Function. In the mammalian organism, the antidiuretic principle of the posterior pituitary is a hormone concerned with water metabolism. This conclusion is based upon various types of evidence. In human beings, lesions of the posterior pituitary are sometimes associated with a condition known as diabetes insipidus. This syndrome is characterized by an abnormally high urine volume due to an inability of the renal tubules to reabsorb a normal percentage of the glomerular filtrate. In this condition, urine volumes as high as 20 liters per day are not uncommon. Also, it has been established by the extensive investigations of Ranson and his coworkers (*see* Fisher, Ingram and Ranson, 1938) that surgical removal of the posterior pituitary in experimental animals leads to a lasting polyuria which resembles the clinical condition of diabetes insipidus. Equally convincing is the fundamental observation of Starling and Verney (1924–1925) that the kidney of a heart-lung-kidney preparation is unable to excrete urine having an osmotic pressure higher than that of the blood unless posterior pituitary extract is added to the perfusion fluid.

The second type of evidence which establishes the rôle of the posterior pituitary in water metabolism is obtained from observations on the effects of the injection of the antidiuretic principle. When posterior pituitary extract is given either to individuals with diabetes insipidus, or to hypophysectomized animals, normal renal function is re-

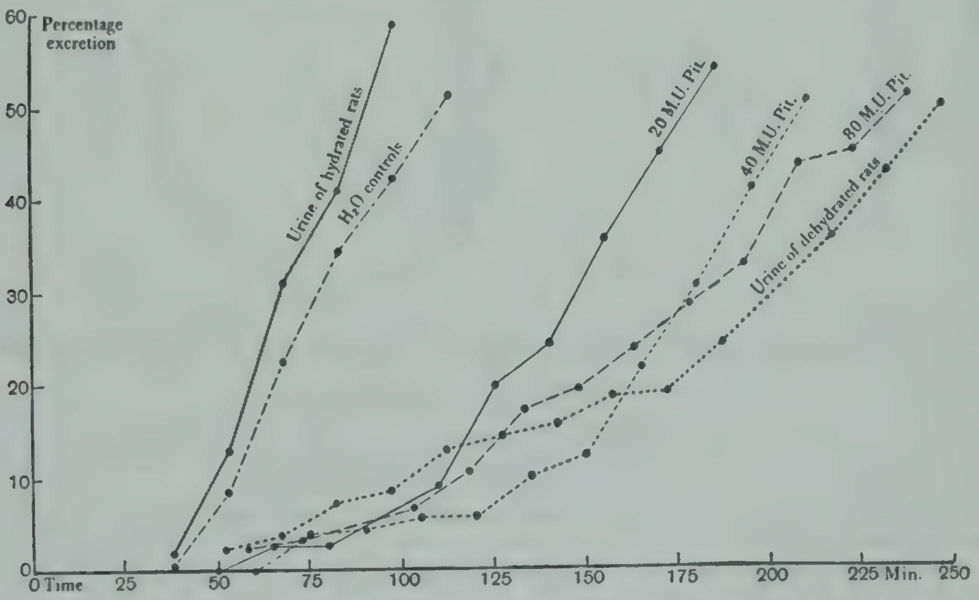


FIGURE 71. *The effect of posterior pituitary solution and the urine of dehydrated rats on water diuresis.*

Antidiuretic potency assayed in standardized rats hydrated with an amount of water equal to 10 per cent of their body weight. Rats receiving no drug (H_2O controls) eliminate 50 per cent of the administered water in about 100 minutes; the subcutaneous injection of as little as 20 milli-units (M.U.) (0.020 unit) of posterior pituitary extract markedly delays the onset of diuresis. A substance behaving like the antidiuretic principle of the posterior pituitary is excreted in the urine of rats dehydrated by water deprivation for 72 hours, but is absent in the urine of hydrated rats. (After Gilman and Goodman, 1937. Courtesy of the *Journal of Physiology*.)

stored. Furthermore, water diuresis can be inhibited by small doses of posterior pituitary. This suggests that tubular reabsorption of water in the kidneys is controlled, at least in part, by the secretory activity of the posterior pituitary. In support of this concept, it has been shown that an antidiuretic substance, presumably of pituitary origin, is excreted in the urine where its concentration varies directly with the body need for water conservation (Gilman and Goodman, 1937) (Figure 71).

The sensitivity of the response to the antidiuretic principle likewise supports its hormonal nature. Theobald (1934) has shown that a total dose of 0.005 units of posterior pituitary extract in man will inhibit water diuresis. A unit is the activity of 0.5 milligram of dried posterior pituitary powder. When one considers that the chemically pure hormone must represent only a very small percentage of the dried gland, the remarkable sensitivity of the kidney to this agent will be appreciated.

Finally, glandular cells of a secretory nature have been demonstrated in the posterior hypophysis by Gersh (1939). The activity of these cells, as judged histologically, varies with the degree of body hydration. The evidence suggests that these are the cells which elaborate the antidiuretic hormone.

Mechanism of Antidiuretic Action. The site of action of the antidiuretic substance is thought to be the loop of Henle of the renal tubule. Phylogenetic

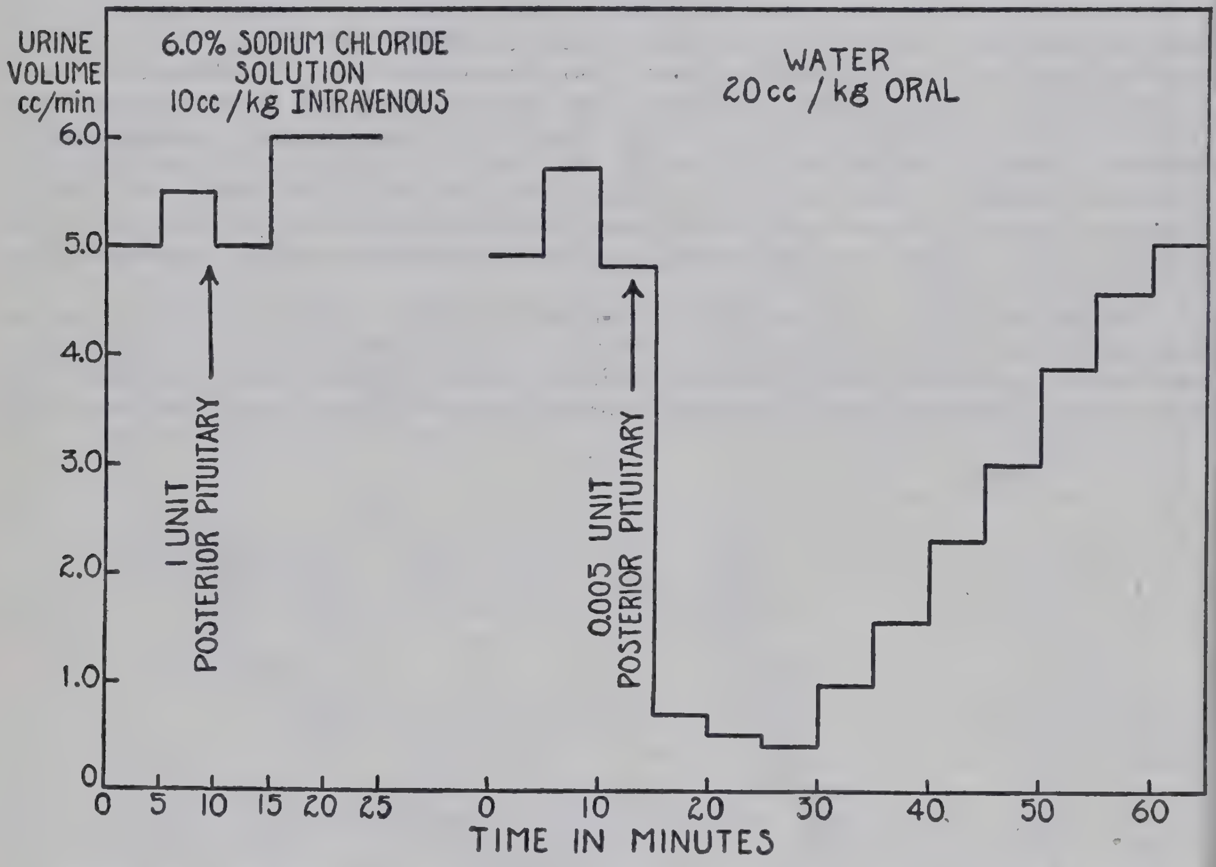


FIGURE 72. *The effect of solution of posterior pituitary in unanesthetized dogs on the diuresis induced by water and hypertonic sodium chloride solution.*

The rate of urine flow per minute for consecutive five minute periods is shown by the level of the horizontal segments of the figures. *Right:* The urine excreted following the ingestion of water is dilute in composition and has a low osmotic pressure. In response to the intravenous injection of as little as 0.005 unit of solution of posterior pituitary the renal tubules are stimulated to reabsorb water to the limit of their physiological capability. As a consequence, the rate of urine flow is markedly reduced. Note the immediacy of the response. The effect can be prolonged by increasing the dose.

Left: The diuresis obtained after the intravenous injection of hypertonic sodium chloride solution is mainly due to the osmotic effect of the sodium chloride in the tubular urine which limits the reabsorption of fluid. Despite the rapid rate of urine flow, the tubules are reabsorbing water to the limit of their physiological capacity for reasons explained in the text. Therefore the intravenous injection of posterior pituitary solution, even in doses 200 times as great as that effective in inhibiting water-induced diuresis, does not affect the rate of urine flow.

evidence, extensively reviewed by Marshall (1934), has localized the site of osmotic work in the reabsorption of water in the cells of the loop of Henle. The antidiuretic hormone supposedly is essential for these cells to reabsorb water to their maximal capacity. At this point it should be emphasized that the injection of antidiuretic principle does not increase the *capacity* of the tubular cells to do osmotic work. If a normal kidney is already excreting a maximally concentrated urine, the action of additional posterior pituitary substance is not detectable.

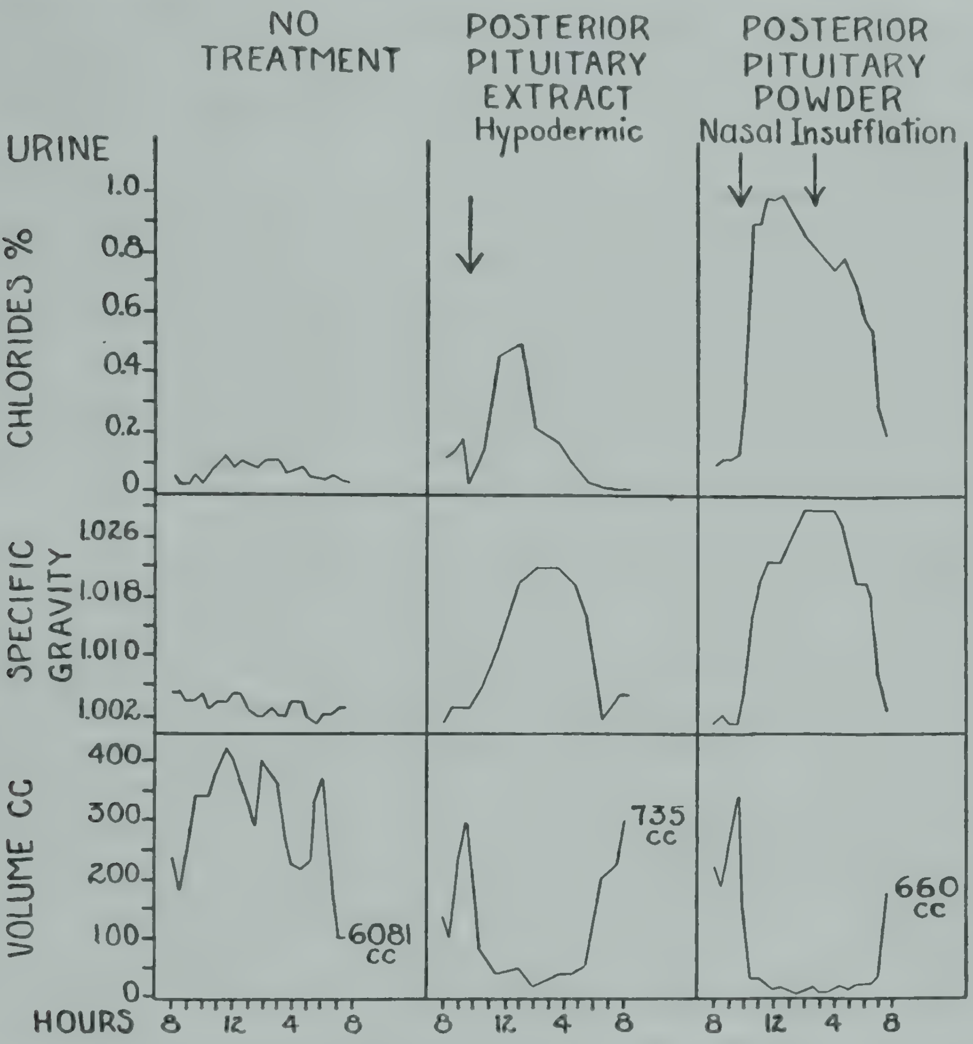


Figure 73. *The control of the polyuria of diabetes insipidus with solution of posterior pituitary.*

Female, aged 21, idiopathic diabetes insipidus, low salt diet. The subcutaneous injection of solution of posterior pituitary (0.5 cc) or the nasal insufflation of posterior pituitary powder (40 mgm) reduces the urine volume to normal limits. Note the rise in chloride content and specific gravity of the urine, indicating that tubular reabsorption of water is greatly increased. The effects of a single dose last from six to ten hours. The advantages of intranasal insufflation are ease of application, economy in cost and absence of side-effects. (After Smith, 1934. Courtesy of *The Journal of the American Medical Association.*)

Thus, the antidiuretic hormone will inhibit a water diuresis, but it is ineffective against a salt or urea-induced diuresis, for the kidney is concentrating the salt or urea to its maximal ability (Figure 72).

Not only the osmotic diuretics but also the xanthines and mercurials counteract the antidiuretic action of posterior pituitary extract. This may be taken as added evidence that the site of action of the xanthine and mercurial diuretics is the renal tubule.

Diuretic Action. In addition to its antidiuretic action, the posterior pituitary principle may sometimes cause diuresis. In fact, the diuretic action was the first to be discovered. It is now considered a secondary and unimportant effect which can only be observed under special conditions in certain species, notably the rabbit. A huge dose of posterior pituitary extract is necessary to elicit a diuretic response in comparison with that required for antidiuresis. Diuresis is probably secondary to changes in renal blood flow and may be the result of a constriction of the efferent arterioles of the glomerulus and an accompanying increase in glomerular filtration pressure. Finally, it is transitory and is followed by prolonged antidiuresis.

Electrolyte Excretion. There is some evidence that the antidiuretic principle may also be concerned with the excretion of salts. This is based upon the finding that accompanying its action the urine contains a high concentration of chloride. Thus, despite the fall in volume of urine, more chloride is excreted per unit of time during posterior pituitary antidiuresis than previously.

Preparations. The antidiuretic principle is available only together with the pressor principle of the posterior pituitary. Indeed, they may be the same substance, the vasopressor action being a fortuitous response to doses which are many hundred times in excess of the minimal effective amount for antidiuresis, but their identity has been questioned (page 662). The commercial posterior pituitary preparations are not assayed for their antidiuretic potency, but for their pressor or oxytocic activity. Those which have antidiuretic activity are *Posterior Pituitary,* U.S.P., *Solution of Posterior Pituitary,* U.S.P., and *Pitressin,* N.N.R. These preparations and their bio-assay are described elsewhere (page 666).

Therapeutic Uses. The only valid therapeutic use of the antidiuretic principle of the posterior pituitary is for the control of polyuria of diabetes insipidus. It is a specific therapy in this condition, in that it corrects a deficiency, and its effects are dramatic. Parenteral administration is necessary. Although the minimal effective dose is low, the ability of the body to destroy the antidiuretic principle necessitates the administration of fairly large amounts. The injection of five to 10 units morning and evening usually completely controls polyuria and polydipsia. Hypodermic administration may be circumvented by taking advantage of absorption by the nasal mucosa (Figure 73). Cotton pledgets moistened with posterior pituitary solution or pitressin may be inserted into the nostrils for several minutes, two or more times a day. A much more convenient technic has been devised by Vidgoff (1932) who demonstrated that the dry posterior pituitary powder itself is effective when applied in minute amounts to the nasal mucosa with the tip of the finger (also *see* Smith, 1934). This may be repeated two or three times daily.

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SECTION IX

DRUGS ACTING ON THE REPRODUCTIVE ORGANS

In this section, the oxytocics, uterine sedatives and hemostatics, abortifacients, and spermatocides are discussed. The drugs of endocrine origin affecting the reproductive system are treated elsewhere.

CHAPTER 36

OXYTOCICS

ERGOT, ERGOT ALKALOIDS AND POSTERIOR PITUITARY

Oxytocics are drugs which stimulate the motility of the uterus. Although much is known about the physiology of the uterus, factors controlling uterine motility are incompletely understood. The uterus contains smooth muscle which exhibits all the properties characteristic of this type of tissue. The organ contracts spontaneously and rhythmically even in its prepuberal state. When the uterus is fully developed, contractions are more marked and its activity varies with different periods of the menstrual cycle. The pregnant uterus is a very motile organ and at term the uterine contractions play an important rôle in the expulsion of the fetus. It is not known, however, what constitutes the stimulus for the initiation and perpetuation of the extreme uterine activity which characterizes labor.

The uterus receives both cholinergic and adrenergic autonomic fibers, the former from the pelvic nerve and the latter from postganglionic fibers from the inferior mesenteric and hypogastric ganglia. However, the responses of the uterus to the stimulation of these nerves and to autonomic drugs are not marked and vary in different species and in the pregnant and nonpregnant state. In human beings, the stimulation of both sympathetic and parasympathetic nerves produces increased uterine motility. The response is more prominent in the pregnant uterus. Nevertheless, complete denervation of the uterus causes little or no change in motor activity. For practical purposes, one may dismiss the action of autonomic drugs upon the uterus as unimportant.

There is, however, a group of drugs which have a pronounced effect on uterine motility. Their action is quite selective for, although other smooth muscles are stimulated, uterine excitation is much more pronounced. These drugs comprise the clinical *oxytocics*. The most important are three alkaloids obtained from ergot, *ergotoxine, ergotamine,* and *ergonovine* (*ergometrine*), and the *oxytocic principle* extracted from the posterior lobe of the hypophysis. In addition, *histamine* and *quinine* have a marked effect on uterine muscle. This does not, by any means, complete the list of drugs which can affect uterine motility but, with the exception of histamine, the aforementioned drugs are those which are used clinically for their oxytocic action.

ERGOT AND THE ERGOT ALKALOIDS

Source. *Ergot* (*Claviceps purpurea*) is a fungus which grows upon rye and other grains. The parasitic nature of ergot was not appreciated until the nineteenth century; before that time it was looked upon merely as being diseased rye. The parasite is especially prevalent during moist, warm weather and can be found in the grain fields of North America and Europe.

The spores of ergot are carried by insects or the wind to the ovaries of young rye where they germinate into hyphal filaments. These filaments secrete a ferment which enables the fungus to penetrate the basal portions of the ovary. The decomposition product resulting from this enzymatic action is a yellow mucoid material called honeydew which was at one time erroneously thought to be the active substance of ergot. The honeydew attracts insects and in this way the fungus is further disseminated. As the hyphal filaments penetrate deep into the ovary of the rye, a dense tissue forms. This tissue gradually consumes the entire substance of the grain and hardens into a purple, curved body called the *sclerotium*. It is this sclerotium which is the source of commercial ergot. It is either picked by hand or separated from the grain by a special threshing process. The gathering of ergot is a peasant industry in many European countries. It is said that the ergot obtained from Spain is the best variety.

Constituents of Ergot. Ergot has been termed a "veritable treasure house of pharmacological constituents." The pharmacologically active substances which have been isolated from ergot have been divided by Barger (1931) into two main groups. In the first group are those products which are peculiar to ergot and not obtainable from any other source. The second group consists of a large number of compounds which can be isolated from ergot but are also obtainable elsewhere. The important members of the first group are the ergot alkaloids. At least ten of these have been definitely identified, the more important of which are *ergotoxine, ergotamine,* and *ergonovine* (*ergometrine*). In addition, there are certain pigments peculiar to ergot without pharmacological significance. A heterogeneous collection of compounds forms the second group. Included are inorganic constituents, carbohydrates, glycerides, sterols, acids, amino acids, amines and bases. The amines and bases are of pharmacological importance. Ergot contains amines which result from the decarboxylation of six amino acids—leucine, tyrosine, histidine, lysine, arginine, and ornithine. It is known that bacteria are capable of effecting the decarboxylation of amino acids, and it is thought that a similar property of fungi may account for the presence of amines in ergot. At least three amines are of pharmacological importance. They are histamine, tyramine and isoamylamine. The pharmacologically active bases found in ergot are choline and acetylcholine.

History. The contamination of an edible grain by a poisonous, parasitic fungus spread death and destruction for centuries. As early as 600 B.C., an Assyrian tablet alluded to a "noxious pustule in the ear of grain," and in one of the sacred books of the Parsees (400–300 B.C.) the following pertinent passage occurs, "Among the evil things created by Angro Maynes are noxious grasses that cause pregnant women to drop the womb and die in childbed." It was fortunate for the Greeks, who objected to the "black malodorous product of Thrace and Macedonia," that they did not eat rye. This grain was also comparatively unknown to the Romans for rye was not introduced into Southern Europe until after the beginning of the Christian era. Consequently there is no undisputed reference to ergot poisoning in the early Greek and Roman literature.

It was not until the Middle Ages that written descriptions of ergot poisoning first appeared although it is probable that the disease was prevalent long before this time. Strange epidemics were described in which the characteristic symptom was gangrene of the feet, legs, hands and arms. In severe cases, drying and blackening of the tissues occurred and the mummified limbs broke off without loss of blood. Limbs were said to be consumed by the Holy Fire and blackened like charcoal. Mention was also made of agonizing burning sensations in the extremities. The disease was called Holy Fire or St.

Anthony's fire, the latter name being in honor of the saint at whose shrine relief was said to be obtained. The relief which followed migration to the shrine of St. Anthony was probably a real one, for the peasants who developed their symptoms as a result of ingesting contaminated grain obtained a complete change of diet during their sojourn at the shrine. The symptoms of ergot poisoning were not restricted to the limbs. Indeed, a frequent complication of ergot poisoning was abortion. A convulsive type of ergotism was also known. There still is no proved explanation as to why, in certain instances, ergotism was associated with symptoms referable to the central nervous system. It has been suggested that the convulsive form of ergotism occurred in persons with vitamin deficiency.

It was not until 1670 that ergot was proved to be the cause of the destructive epidemics which, for centuries, had raged uncontrolled. At present, our knowledge of the etiology of ergot poisoning makes its prevention quite simple. Yet, outbreaks of ergot poisoning have occurred in the present century, epidemics having been reported in Russia in 1926 and in Ireland in 1929.

A fungus growing on corn and causing "corn-smut" (*Ustilago maydis*) is analogous to that found on rye and has been the cause of small outbreaks of maize poisoning, especially in the northern Mediterranean countries.

Ergot was known as an obstetrical herb before it was identified as being the cause of St. Anthony's fire. It was mentioned as early as 1582 by Lonicer as a proved means of producing pains in the womb. For years it was used by midwives before it was recognized by the medical profession. The first physician to employ ergot was Desgranges, but he did not publish his observations until 1818. Before that time, a letter published by John Stearns (1807) in the *Medical Repository* of New York entitled, "Account of the Pulvis parturiens, a Remedy for quickening Child-birth," marked the introduction of ergot into official medicine (Thoms, 1931). This communication is of sufficient historical interest to quote certain pertinent portions of it: "It (Pulvis parturiens) expedites lingering parturition and saves to the accoucheur a considerable portion of time, without producing any bad effects on the patient. . . . Previous to its exhibition it is of the utmost consequence to ascertain the presentation . . . as the violent and almost incessant action which it induces in the uterus precludes the possibility of turning. . . .

"If the dose is large it will produce nausea and vomiting. In most cases you will be surprised with the suddenness of its operation; it is, therefore, necessary to be completely ready before you give the medicine. . . . Since I have adopted the use of this powder I have seldom found a case that detained me more than three hours. . . ."

The use of ergot in the United States spread rapidly, but its adoption in Europe was delayed, perhaps, as Barger (1931) has suggested, because the Old World had suffered too much from the poisonous properties of ergot. The dangers attending the use of the drug, however, were soon recognized. In 1824, Hosack wrote that the number of stillborn children had increased so greatly since the introduction of ergot that the medical society of New York instituted an inquiry. Said Hosack, "The ergot has been called . . . *pulvis ad partum;* as it regards the child, it may, with almost equal truth, be denominated the *pulvis ad mortem.*" This astute observer recommended that the drug be used only to control postpartum hemorrhage. Thus, more than a century ago, the indications and contraindications of the oxytocic drugs were defined.

Chemistry. Ergot has been the object of intensive chemical investigation for many years. It is now believed that all the activity of crude ergot can be accounted for by the chemically identified products obtainable from it. Tanret, in 1875, was the first to isolate an ergot alkaloid now known as *ergotinine.* This substance, however, proved to be inactive. Barger and Carr (1906) obtained a pharmacologically active crystalline alkaloid, *ergotoxine.* In the same year, Kraft independently obtained the identical substance and thought it to be a hydrated form of ergotinine. It is now known that ergotinine and ergotoxine are optical isomers, the latter being levorotatory. In 1920 Stoll announced the discovery of two more alkaloids of ergot, *ergotamine* and *ergotaminine.* These two substances are also optical isomers. Ergotamine is levorotatory and pharmacologically active; ergotaminine is dextrorotatory and inactive.

With the isolation of these four alkaloids, two of them showing a high degree of activity and the typical actions of crude ergot extracts, it was assumed that the chemical riddle of crude ergot had been solved and that the actions of ergot were due to these known alkaloids. As time passed, however, it gradually became apparent that the pharmacological properties of fluidextract of ergot were quite different from those of its pure alkaloids. The crude preparation was often more efficient, being more rapid in action and effective after oral ingestion. In contrast, the crystalline products which it yielded acted only after a latent period and were relatively impotent by the oral route. Once again the problem of the chemistry of ergot was attacked, this time with such vigor that four groups of investigators independently and almost simultaneously announced the discovery of a new ergot alkaloid. Dudley and Moir (1935), Thompson (1935), Stoll and Burckhardt (1935), and Kharasch and Legault (1935) named the alkaloids which they had isolated *ergometrine, ergostetrine, ergobasine* and *ergotocine,* respectively. It was soon ascertained that these workers were dealing with the same substance, to which the Council on Pharmacy and Chemistry gave the name *Ergonovine* (1937). Ergonovine is levorotatory, and its dextroisomer, *ergometrinine,* has also been isolated.

Table 34

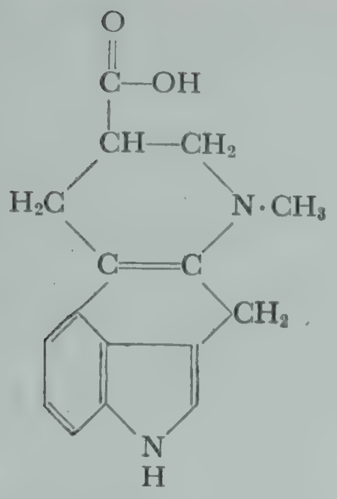
THE ALKALOIDS OF ERGOT

Alkaloid	Empirical Formula	Optical Rotation
* Ergotoxine (1906)	$C_{35}H_{39}O_5N_5$	Levo
Ergotinine (1875)		Dextro
* Ergotamine (1920)	$C_{33}H_{35}O_5N_5$	Levo
Ergotaminine		Dextro
* Ergonovine (1935)	$C_{19}H_{23}O_2N_3$	Levo
Ergometrine		
Ergobasine		
Ergotocine		
Ergostetrine		
Ergometrinine (1936)		Dextro
Ergosine (1936)	$C_{30}H_{37}O_5N_5$	Levo
Ergosinine		Dextro
Ergocristine (1937)	$C_{33}H_{35}O_5N_5$	Levo
Ergocristinine		Dextro

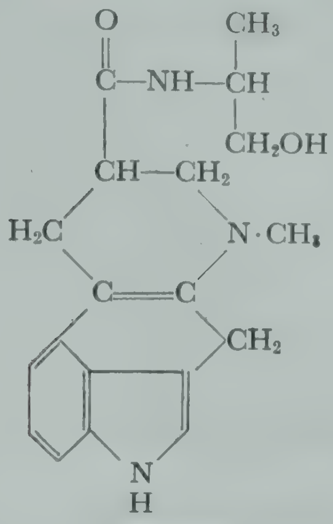
* Pharmacologically active compounds used in therapeutics.

In 1936, Smith and Timmis isolated another pair of ergot alkaloids, *ergosine* (levorotatory) and *ergosinine* (dextrorotatory). In 1937, Stoll and Burckhardt added *ergocristine* (levorotatory) and *ergocristinine* (dextrorotatory) to the growing number of pairs of ergot alkaloids.

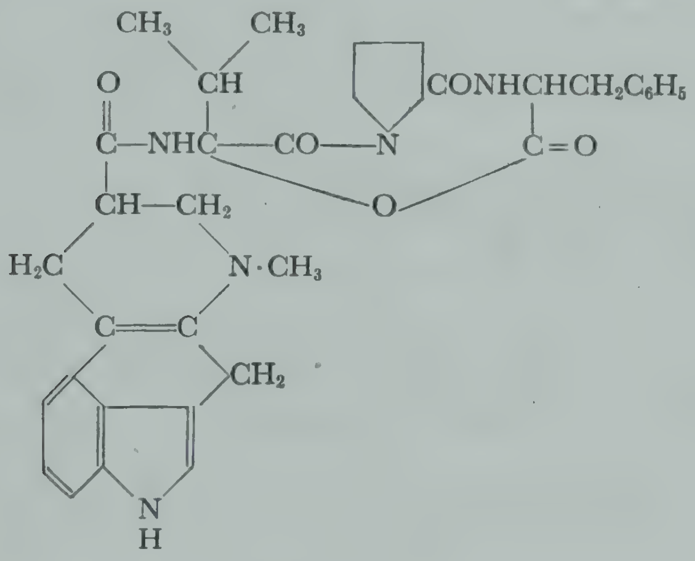
The chemical structure of the alkaloids of ergot has been elucidated largely by the work of Jacobs and his collaborators (*see* review of Nelson and Calvery, 1938). All are derivatives of lysergic acid, an indole derivative. The optical isomerism of the alkaloids of ergot is due to the presence of an asymmetric carbon atom in the lysergic acid portion of the molecule. Only the levorotatory member of each pair possesses marked pharmacological activity. Ergonovine upon hydrolysis yields lysergic acid and hydroxy isopropylamine. The alkaloids of higher molecular weight hydrolyze to ammonia, a keto-acid and two amino acids in addition to lysergic acid. The empirical formulas of several pairs of ergot alkaloids are given in Table 34. The probable structural formulas of lysergic acid, ergonovine and ergotoxine are as follows:



Lysergic Acid



Ergonovine
(Ergometrine)



Ergotoxine

Pharmacological Actions of Ergotoxine and Ergotamine. The pharmacological actions of ergotoxine and ergotamine are so nearly identical that they will be discussed together. Ergonovine, on the other hand, is quite distinct in several important respects and will therefore be given separate consideration.

Uterus. The most important action of ergotoxine and ergotamine is on the uterus. The effects of the two alkaloids on this organ are identical. The motor activity of the uterus is markedly increased. The type of contraction exhibited is related to the dose of drug administered. After small amounts, uterine contractions are quite normal in character and are followed by relaxation. After large doses, the contractions are more powerful and spastic in nature. The sensitivity of the uterus to ergot alkaloids varies, especially with the degree of maturity and the stage of gestation. Even an immature uterus is stimulated by the drugs. The gravid uterus, however, is much more sensitive and when small doses of ergot alkaloids are given at term or immediately postpartum it is possible to obtain a marked uterine response unaccompanied by any side-actions. There is little doubt that the mechanism of action is a direct muscular stimulation, and the isolated uterus responds equally as well as the uterus *in situ.*

Other Smooth Muscle. The action of ergotoxine and ergotamine on the uterus is quite selective because all smooth muscles are not similarly affected. For example, the action on gastro-intestinal motility is negligible. In some animals, notably the cat, ergot alkaloids cause marked miosis due to a direct action on the sphincter muscle of the iris.

Circulatory System. Following the administration of large doses of ergotoxine or ergotamine, there is an increase in blood pressure which results from constriction of the smaller blood vessels. The site of this action is peripheral for vasoconstriction occurs after section of the vasomotor nerves. In all probability, the action is a direct muscular one. Ergotoxine and ergotamine also have some effect on the heart, therapeutic doses usually causing a noticeable bradycardia. This may be a reflex response to the vasoconstriction. On the other hand, these alkaloids possess, to a significant degree, the property of inactivating cholinesterase and their action in slowing the heart may, in part, be similar to that of physostigmine.

Ergotamine and ergotoxine damage the capillary endothelium. The mechanism of this toxic action is not understood. Vascular stasis, thrombosis and gangrene result and cause the prominent features of ergot poisoning. When the alkaloids are injected into roosters, the comb and wattles become cyanotic and cold, and eventually gangrenous. This vascular phenomenon provides the basis for the U.S.P. bio-assay of ergot. The susceptibility of different species to gangrene produced by ergot varies greatly. Man is peculiarly sensitive.

Sympathetic Nervous System. Ergotoxine and ergotamine paralyze the excitatory responses to epinephrine and adrenergic nerve impulses. This phenomenon is fully discussed elsewhere (pages 340, 482).

Central Nervous System. The action of ergotoxine and ergotamine on the central nervous system is variable and, as a rule, unimportant. Small doses may mildly stimulate the respiratory center. In the laboratory, the intravenous injection of large amounts of the alkaloids in anesthetized animals is likely to cause respiratory arrest due to medullary depression. After toxic doses in man, vomiting is a frequent symptom. The cause is not understood. Large doses of ergotoxine and ergotamine given intravenously in certain laboratory animals produce marked excitement, sham rage and other evidence of stimulation of central sympathetic centers.

Absorption, Fate and Excretion. Little is known of the fate and excretion of the ergot alkaloids. Information on the rate of absorption, however, has accumulated from clinical observations. Ergotoxine and ergotamine are poorly and irregularly absorbed from the gastro-intestinal tract. The effective oral dose is three to four times the intramuscular dose, and even then the resulting action is unpredictable (Figure 74). There is a latent period of approximately twenty minutes between the intramuscular injection of the drugs and the onset of uterine response. The action is quite long in duration, however, and may persist for several hours.

Ergonovine (Ergometrine). Ergonovine shares with ergotamine and ergotoxine the property of causing uterine stimulation, and the character of the uterine contractions which it produces does not differ from that described previously. Ergonovine, however, is much more rapid in action for the uterine response occurs almost immediately after intravenous injection of the drug and within a few minutes after intramuscular or oral administration. Ergonovine thus differs from ergotoxine and ergotamine in that it is readily absorbed from the gastro-intestinal tract. The sensitivity of the uterus to ergonovine is very great, and in pregnant women an intravenous dose of as little as 0.1 mgm or an oral dose of only 0.25

mgm results in a marked response. The action of the drug persists for several hours (Figure 74).

The effects of ergonovine on sympathetically innervated structures are in sharp contrast to those of ergotoxine and ergotamine. Ergonovine is not sympatholytic, and it appears to stimulate certain effector organs in a manner similar to sympathomimetic drugs. For example, it causes mydriasis after instillation into a rabbit's eye, vasoconstriction when perfused through a frog's limb, and relaxation of the isolated rabbit intestine. On the other hand, unlike a true sympathomimetic drug, ergonovine causes little or no rise in blood pressure when injected intravenously in anesthetized cats and dogs.

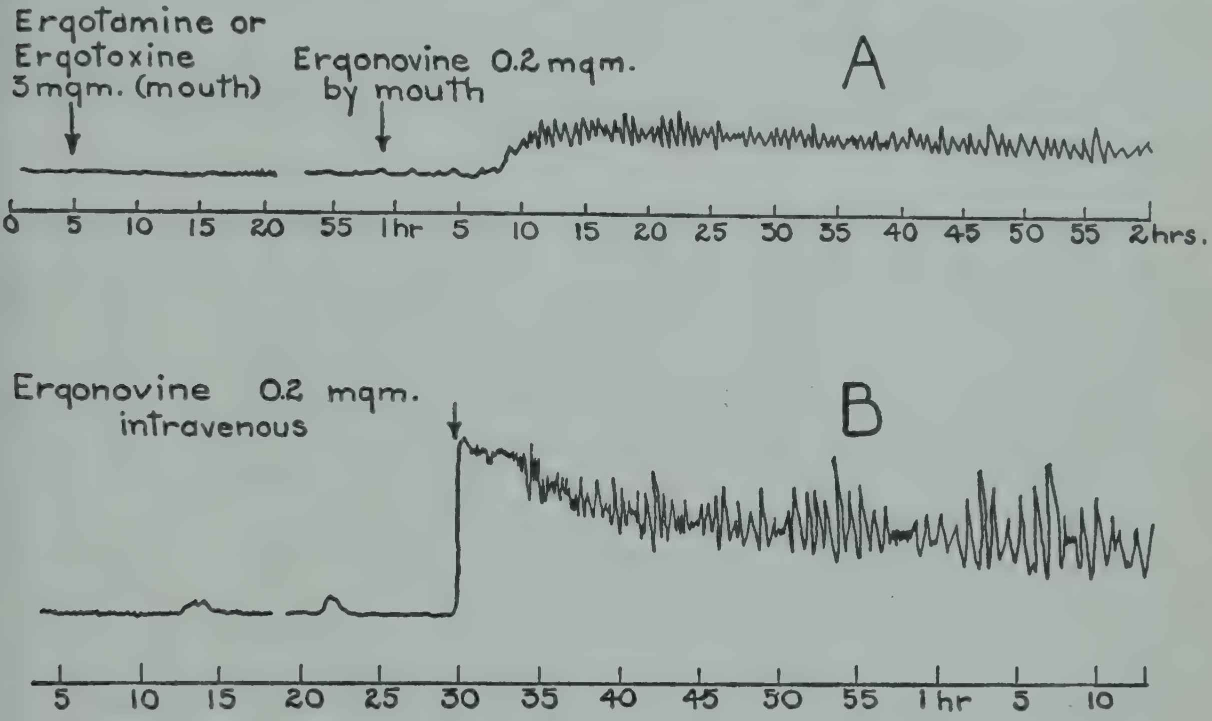


FIGURE 74. *The effect of ergonovine on the human uterus.*

A. The effect on the human uterus of 3 mgm of orally administered ergotamine or ergotoxine as compared with 0.2 mgm of ergonovine. The record is that of the uterine motility of a woman (para 4) seven days post partum, obtained by means of a balloon and manometer. Note the inefficacy of ergotoxine and ergotamine when given by mouth and the prompt and sustained response to the small dose of ergonovine. *B.* The effect of 0.2 mgm of ergonovine, given intravenously, on the uterine motility of a woman (para 2) seven days post partum. Note the immediate, marked and sustained response. (After Davis, Adair and Pearl, 1936. Courtesy of *The Journal of the American Medical Association.*)

Ergonovine shares with ergotoxine and ergotamine the ability to produce gangrene. In the case of ergonovine, however, this property has been demonstrated only in experimental animals. There have been no clinical reports of the occurrence of gangrene in human beings following the use of ergonovine. The acute toxicity of ergonovine in animals is only about one-quarter that of ergotoxine and ergotamine. The pharmacology of ergonovine has been investigated, especially by Brown and Dale (1935), and has been reviewed by Smith (1938).

Fluidextract of Ergot. The clinical importance of fluidextract of ergot has diminished since the discovery of ergonovine. Prior to 1935, the fluidextract was often employed because it was the only type of ergot preparation which was active by mouth, and also because it had a more rapid onset of action than the pure alkaloids available up to that time. It had the disadvantage of being unstable and very liable to deterioration. It is now appreciated that the desirable properties of the fluidextract are due mainly to the presence of ergonovine. Ergonovine, now being clinically available, promises largely to replace the fluidextract of ergot in obstetrical therapy.

Bio-assay. Fluidextract of ergot varies in its alkaloidal content, depending on the activity of the dried ergot used in its preparation. It therefore must be assayed in order to standardize its potency. As has already been stated, the action on the cock's comb forms the basis of the U.S.P. assay. The fluidextract is standardized against crystalline ergotoxine ethanesulfonate so that one cc of the former is equivalent to 0.5 mgm of the latter. In Great Britain, *Liquid Extract of Ergot* (B.P.) is chemically standardized to contain 0.06 per cent of the total alkaloids of ergot.

Ergot Poisoning. The ergot alkaloids are highly toxic and may cause acute or chronic poisoning. Acute poisoning is rare and usually results from the ingestion of large amounts of ergot preparations in attempts at abortion. The symptoms consist of vomiting, diarrhea, unquenchable thirst, tingling, itching and coldness of the skin, a rapid and weak pulse, confusion and unconsciousness.

Chronic poisoning is more common. At present the epidemic form of ergot poisoning arising from the ingestion of contaminated grain is seldom seen. However, the alkaloids of ergot are extensively employed in therapeutics, and poisoning from their injudicious administration is not rare. Poisoning is usually due to overdosage. There are indications, however, that increased sensitivity to ergot alkaloids may accompany febrile and septic states and diseases of the liver. Thus many cases of ergot poisoning have been reported in patients with puerperal fever. Also several fatalities from gangrene have occurred in patients with liver damage who received ergotamine for relief of the accompanying pruritus. Apparently in such cases there is unusual vascular sensitivity to ergotamine, because the drug has been extensively employed in the treatment of migraine without serious toxic manifestations. The presence of peripheral vascular disease also constitutes a contraindication to the use of the ergot alkaloids. Fatal poisoning has occurred after the oral administration of 26 mgm of ergotamine over a period of several days, and also following single injections of only 0.5 to 1.5 mgm.

Circulatory symptoms are the first to become evident. Gangrene starts in the extremities, usually in the toes but also in the fingers. Two factors are involved in the impairment of the circulation. Vasoconstriction is one of these but this alone is not sufficient to cause the marked vascular stasis which is observed. Lesions of the intima also develop and result in thrombi which may completely occlude the smaller arteries. A detailed description of the pathological changes observed in blood vessels following clinical ergot poisoning has been given by Yater and Cahill (1936). Circulatory disturbances other than those associated with vascular injury have been reported. Anginal pain, tachycardia or bradycardia, and elevation or lowering of the blood pressure may occur.

In addition to circulatory disturbances, other symptoms of ergot poisoning appear. The most common of these are headache, nausea, vomiting, diarrhea and dizziness. Also there may be noticed weakness, formication, itching, and coldness of the skin. Symptoms referable to the central nervous system are confusion, depression, drowsiness, convulsions, hemiplegia, and tabetic manifestations. In some patients, a fixed miosis may be seen.

Treatment. The treatment of ergotism consists in complete withdrawal of the offending drug and symptomatic measures. The latter especially include attempts to maintain an adequate circulation to the affected parts. Vasodilators such as the choline esters, nitrites and especially papaverine may be tried. If gangrene impends, passive vascular exercise or intermittent venous occlusion may be resorted to in addition to the usual mechanical and surgical procedures. Nausea and vomiting may be relieved by atropine. Therapy of the milder toxic symptoms seen after ergotamine is discussed on page 486.

Preparations. *Ergot,* U.S.P., B.P., is the dried sclerotium of *Claviceps purpurea.* It is not prescribed as such. *Fluidextract of Ergot,* U.S.P. (*Liquid Extract of Ergot,* B.P.), has been described above. It is the preparation of choice among the galenicals. *Prepared Ergot,* B.P., and *Extract of Ergot,* N.F., are inferior to the fluidextract. *Ergot Aseptic,* N.N.R., is a liquid extract of ergot prepared for parenteral administration and marketed in ampules containing one cc of sterile solution. The potency of the product is adjusted to be the same as the official fluidextract.

The purified alkaloids of ergot are also available for therapeutic use. *Ergotamine tartrate* consists of colorless crystals soluble in water to the extent of 1:500. It is marketed as *Gynergen,* N.N.R., and is available in 0.5 and 1.0 cc ampules, containing 0.25 and 0.5 mgm of the drug, respectively, as a 0.1 per cent solution and in tablets containing 1.0 mgm each. *Ergotoxine Ethanesulfonate,* B.P., is seldom used in the United States. It is included in the U.S.P. only as a reference standard. It consists of a colorless, crystalline compound, sparingly soluble in water. *Ergonovine* (*Ergometrine,* B.P.) is a colorless, crystalline substance slightly soluble in water. It is not an official drug in the United States but is available under the name Ergotrate. *Ergotrate-H* is the hydracrylate of ergonovine and is marketed in ampules containing 0.2 mgm of the salt in sterile aqueous solution for intravenous or intramuscular injection. *Ergotrate* is the malate salt and is marketed in tablets containing 0.2 mgm for oral or sublingual administration.

Therapeutic Uses. The actions of the ergot alkaloids on the uterus and blood vessels provide the basis for their chief therapeutic applications. The clinical use of ergot in obstetrics is discussed in conjunction with the other oxytocics (page 667). The use of ergotamine in migraine and certain other disorders is described under the autonomic drugs (page 483).

POSTERIOR PITUITARY

The posterior pituitary is a source of at least two substances possessing marked pharmacological activity. Also, extracts of this gland, when given parenterally, have three distinct actions. They stimulate the uterus (oxytocic action), cause peripheral vasoconstriction (pressor action) and act upon the renal tubules to enhance water reabsorption (antidiuretic action). The extraction of such active substances from a gland of internal secretion has led to the assumption that the extractives are hormones. The hormonal nature of the antidiuretic principle of the posterior pituitary is more firmly established than that of the other active constituents of the posterior lobe (page 647).

The pharmacology of posterior pituitary extract will be described here because many available preparations possess the three aforementioned actions. The fact that the posterior pituitary is discussed under the oxytocic drugs does not minimize the importance of its vasoconstrictor and antidiuretic principles.

Nature and Chemistry. The question whether the pharmacological activity of the posterior pituitary is due to the presence of a single substance or to several substances is still being debated. Kamm and coworkers (1928) separated two active fractions from posterior pituitary extract. One possesses marked oxytocic activity and the other is strongly vasopressor and antidiuretic. The separation is not absolute, however, for each of the two fractions is contaminated by the other to the degree of approximately one per cent. Kamm and his associates, therefore, believe that there are two separate chemical entities responsible for the activity of posterior pituitary extracts. On the other hand, Abel (1930) was of the opinion that a single chemical substance is responsible for all the pharmacological activity and that the apparent separation achieved by Kamm resulted from the breakdown of an original single molecule into two active components. (Also *see* Rosenfeld, 1940.) The vasopressor-antidiuretic principle of the posterior pituitary has been further fragmented by Heller (1939). Heller has shown that the antidiuretic factor is more stable than the pressor factor over a wide pH range, and he has succeeded in preparing solutions of posterior pituitary which retain potent antidiuretic activity but which have lost most of their pressor effect. Heller believes the two actions reside in chemically different principles.

The practical points to be kept in mind are the following. Simple extracts of posterior pituitary always exhibit the three types of activity. There are commercially available products in which either the oxytocic activity or the vasopressor-antidiuretic activity predominates almost to the exclusion of the other. No separation has been made, in commercial preparations, of the vasopressor and antidiuretic principles.

Comparatively little is known of the chemical composition of the active constituents of posterior pituitary. Stehle and Fraser (1935) are of the opinion that they are polypeptides with a minimal molecular weight of approximately 2000, and Stehle and Trister (1939) identified several amino acids in the products of hydrolysis of purified preparations. The activity of pituitary extracts is readily destroyed by hydrolysis with dilute acid or alkali. There is likewise evidence that potency is lost after subjecting pituitary extracts to reducing agents. The enzymes of the gastro-intestinal tract also destroy posterior pituitary principles which are therefore totally ineffective when administered orally.

Pharmacological Actions. *Uterus.* Pituitary extract causes marked stimulation of the uterus. The action is a direct one on the myometrium, and is highly selective. The principle in pituitary extract responsible for uterine stimulation can be separated from the component which causes constriction of the smooth muscle of blood vessels, and has been called the *oxytocic principle* of the posterior pituitary. Several factors modify the response of the uterus to pituitary extract. Whereas small doses merely augment the tone and increase the amplitude of the contractions, further administration of the drug results in uterine tetany lasting five to 10 minutes (Figure 75). The uterus is more sensitive to pituitary extract during the first two weeks of the menstrual cycle. Furthermore, the uterus becomes more reactive as pregnancy progresses (Robson, 1933; Moir, 1934). These alterations in sensitivity are believed to result from the action on the uterus of the ovarian and luteal hormones. Estrone intensifies and progesterone diminishes the response of the uterus to pituitary extract (Bell and Robson, 1938). The two hormones cause a similar variation in the responsiveness of the uterus to the ergot alkaloids.

All portions of the uterus are not equally stimulated by pituitary extract. Newton (1937) showed in experimental animals that the cervix of the uterus does not respond even to high concentrations of the drug. He believes that the coordinated type of uterine contraction involving only the fundus in response to pituitary extract would be efficacious at parturition.

Newton is inclined to believe that the oxytocic principle of the posterior pituitary may play an important physiological rôle in the evacuation of the uterine contents at term. The fact that an extract of the posterior pituitary possesses a strong oxytocic action presents a temptation to assign to the gland an endocrine function important in parturition.

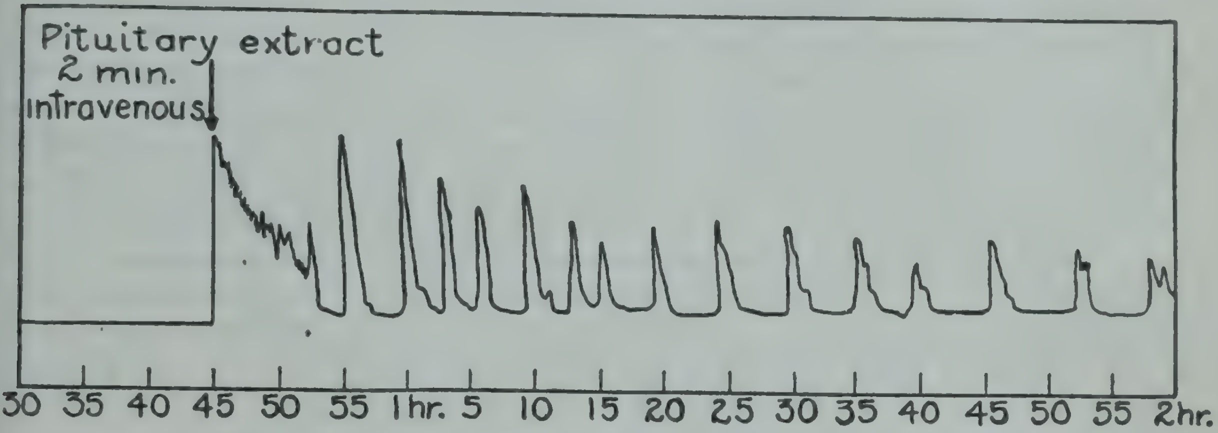


Figure 75. *The effect on the uterus of 0.15 cc of solution of posterior pituitary given intravenously to a woman (para 3) on the sixth day post partum.*

The record is a kymographic tracing of uterine motility obtained by means of a balloon and manometer. The response to solution of posterior pituitary is marked for five or ten minutes, after which normal rhythmic contractions return. The control base line is schematic and does not represent uterine atony before the injection of the drug. (After Davis, Adair and Pearl, 1936. Courtesy of *The Journal of the American Medical Association.*)

There is a great deal of evidence, however, which questions the rôle of the posterior pituitary in parturition. Ivy, Hartman and Koff (1931), experimenting with monkeys, compared the normal contractions of the uterus with those induced by pituitary extract and failed to note similarity. Indeed, the drug caused an hourglass type of contraction and it was concluded that the uterine movements induced by pituitary extract were not calculated to expel the fetus. Allan and Wiles (1932) removed the hypophysis from pregnant cats and normal delivery occurred at term two to eleven days after operation. P. E. Smith (1932) mated rats after removal of the posterior hypophysis and in all cases where pregnancy ensued, delivery was normal and occurred at term. Smith pointed out, however, that anatomical removal of the posterior pituitary may not remove all sites of formation of the oxytocic principle. Regardless of the physiological importance of the oxytocic principle of the hypophysis, it cannot be denied that when employed clinically this extract has a powerful action on the uterus and offers a useful therapeutic tool.

Cardiovascular System. The effect of pituitary extract on the circulation was first described by Oliver and Schäfer in 1895. After injection of the extract into anesthetized animals, they observed a marked rise in blood pressure. The rise is not as great as that produced by epinephrine but is much more sustained. Pituitary extract elevates the blood pressure by a constrictor action on capillaries and arterioles. The *capillaries,* however, respond more markedly. The action is a direct one on the vascular musculature. It is neither antagonized by adrenolytic agents nor prevented by vascular denervation, and is therefore not related to adrenergic vasomotor nerves.

The action of pituitary extract on the *heart* is variable. There is some evidence from studies on the isolated heart that contraction is strengthened. In the intact animal, however, a decrease in coronary blood flow occurs, due to coronary vasoconstriction (Essex and coworkers, 1940), and the heart is depressed as a result of a diminished blood supply. Geiling and Resnik (1925) studied the cardiac changes induced by pituitary extract in unanesthetized dogs and observed a brief period of acceleration of rate followed by profound slowing. During the period of bradycardia, they noticed a marked prolongation of auriculoventricular conduction time and sinoauricular block. Part of this effect was due to a direct myocardial depression for it was not abolished by atropine. The dependence of the pituitary-induced electrocardiographic changes upon alterations in coronary circulation was experimentally demonstrated by Melville (1938).

Reflex slowing of the heart rate also occurs after pituitary extract. This is a compensatory mechanism to offset the effect on blood pressure of peripheral vasoconstriction. The reflex control of blood pressure is obvious when pituitary extract is administered to unanesthetized animals or man. Apparently, the compensatory cardiovascular reflexes are sufficiently depressed by anesthesia to allow a rise in blood pressure to occur, but when pituitary extract is administered to normal subjects no rise in systemic blood pressure is elicited. For example, Kolls and Geiling (1924) found that pituitary extract in unanesthetized dogs actually caused a fall in systolic blood pressure despite capillary constriction. This observation has been amply confirmed. The effects of pituitary extract upon the circulation in man have been carefully studied by Grollman and Geiling (1932) who found that no rise in blood pressure occurred. Immediately following the injection of the drug, the heart rate, oxygen consumption and cardiac output were temporarily diminished. The venous blood became arterial in character and it was concluded that both cardiac and peripheral circulatory effects combined to interfere with the tissue supply of oxygen. As a result there followed an accumulation of metabolites and an oxygen debt. A more lasting increase in cardiac output and oxygen consumption subsequently occurred to compensate for this debt (Figure 76).

The failure of pituitary extract to cause a rise in blood pressure indicates that the cardiovascular reflexes of the body are normally more than competent to com-

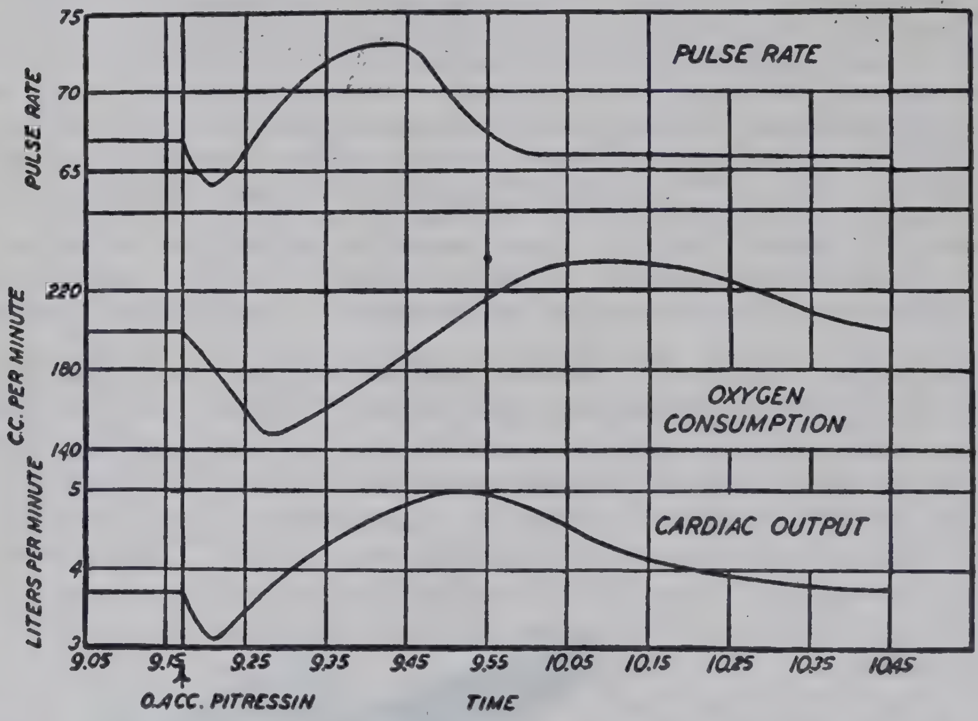


FIGURE 76. *The effect of posterior pituitary extract on cardiac rate and output in a normal adult.*

The pulse rate and cardiac output are decreased below normal for a brief period which is followed by an increase in rate and output of more prolonged duration. Similar changes occur in the oxygen consumption except that both the decrease and increase are more prolonged than in the case of the cardiac functions. See text for explanation of these phenomena. (After Grollman and Geiling, 1932. Courtesy of the *Journal of Pharmacology and Experimental Therapeutics.*)

pensate for the peripheral actions of the drug on the circulation. Thus the pressor response to pituitary extract differs greatly from that to epinephrine. When the latter drug is injected, the heart, as well as the peripheral vessels, is stimulated and cardiac output cannot be adjusted to compensate for increased peripheral resistance to blood flow. The facts cited cast considerable doubt on the clinical value of pituitary extract as an agent for elevating blood pressure.

As has already been stated, Kamm and coworkers succeeded in separating two fractions from the extracts of posterior pituitary. That fraction which is effective in stimulating the musculature of blood vessels and producing the cardiovascular responses described has been called the *pressor principle* of the posterior pituitary. The physiological significance of the pressor principle is obscure. Its rôle as a hormone has yet to be established. No marked circulatory disturbance follows the removal of the posterior pituitary. Some investigators believe that the pressor substance may be concerned in the etiology of vascular hypertension. Indeed, histological evidence has been presented to show that in some cases of essential hypertension there is a proliferation of basophilic cells supposedly concerned with the formation of this principle. Such adenomatous cellular accumulations, however, are noted in the absence of abnormally high blood pressures.

Renal Function. The fraction of pituitary extract which contains the pressor principle also has marked *antidiuretic action.* This is discussed in detail under antidiuretics (page 647).

Intestinal Musculature. The action of posterior pituitary extracts on the motility of the intestinal tract is variable, and there is no unanimity of opinion as to the type of response which occurs. In unanesthetized dogs with intestinal fistulas, Gruber and Robinson (1929) and Quigley and Barnes (1930) observed inhibition of various portions of the intestine after the administration of pituitary extracts. Melville and Stehle (1934) confirmed these observations on isolated intestinal loops, but found that, when the intact gastro-intestinal tract was studied with the use of barium and radioscopy, an entirely different picture was obtained. They found that both the oxytocic and pressor principles of pituitary extract acted upon the intestinal musculature. The pressor principle stimulated the small intestine and colon. Peristaltic contractions were marked and the contents of the small intestine were propelled into the large bowel. When the oxytocic principle was given, the colon was not affected, the circular muscle of the small intestine was relaxed, the longitudinal muscle constricted, and none of the contents of the small bowel passed the ileocecal valve. It is difficult to explain why isolated intestinal loops fail to respond in the typical manner when the normal mechanism of action is, in all probability, a direct stimulation of the intestinal muscle.

The effects of posterior pituitary on the human bowel have been studied by Guthrie and Bargen (1936). They employed subjects with colostomies and recorded the activity of the terminal ileum, transverse colon and sigmoid flexure. The following conclusions were drawn: (1) pituitary extract is a powerful stimulant of intestinal peristalsis, (2) is constant and regular in its action, (3) acts with apparently equal strength on both the colon and the ileum, (4) increases the motility of the intestine apparently without exerting an effect on tonus, and (5) has a rapid onset of action (three to five minutes) and a duration with gradually diminishing effects of from 45 to 90 minutes (Figure 77). The dose employed was 20 units of a preparation containing all the posterior pituitary principles.

Galactagogic Action. Pituitary extract has been termed a galactagogue because it may increase temporarily the amount of milk obtainable from lactating animals. It has no effect on total milk production over extended periods of time, and the transient action is due to stimulation of the smooth muscle of the ducts of the mammary glands resulting in a more complete expression of their contents. This response has also been elicited in human beings but has no clinical value.

Metabolic Effects. The administration of pituitary extracts in high doses to experimental animals increases the blood sugar and lactic acid, and decreases the basal metabolic rate. These actions are poorly understood, are of no practical importance, and need cause no concern in the clinical use of pituitary extract.

Central Nervous System. The effects of pituitary extract upon the central nervous system are not well defined. After large doses, there may be a generalized depression. Cushing (1931) and Light and Bysshe (1933) reported that the injection of the pressor principle into the cerebral ventricles of monkeys and man caused a marked vasodilatation over the blush area before sufficient time had elapsed to allow for absorption of the drug. This response is not evoked by the oxytocic principle, but a similar reaction occurs after the intraventricular injection of pilocarpine. The investigators cited believe that the autonomic centers adjacent to the ventricles are directly stimulated by the pressor principle. The physiological significance of this observation is not yet evident.

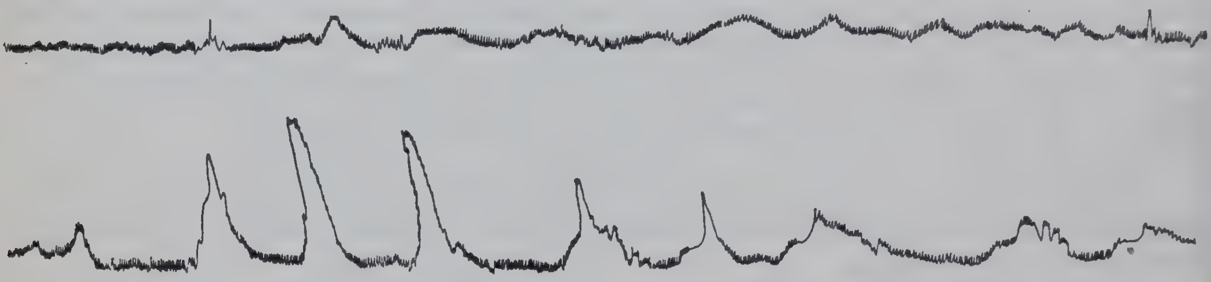


FIGURE 77. *Effects of solution of posterior pituitary on the human colon.*

Kymographic tracings obtained by means of a balloon and tambour in patients with colostomies whose bowels and colonic stomas were functioning normally. The upper record shows the small rhythmic waves of contraction that occur normally in the transverse colon. The lower tracing shows the large waves of contraction that follow the intramuscular injection of 20 units of pituitary extract. Colonic activity appears within three to five minutes after administration of the drug and large powerful contractions occur every three to five minutes. The effects of the drug cease within 45 to 90 minutes. (After Guthrie and Bargen, 1936. Courtesy of *Surgery, Gynecology and Obstetrics.*)

Bio-assay. Extracts of the posterior lobe of the pituitary gland must be assayed by biological methods in order to ascertain their potency. The U.S.P. and B.P. methods of assay depend solely on measuring the oxytocic activity of the extracts. The uterus of the immature guinea pig is used as a test object and the reference substance is a reference powder identical in activity with the International Standard Posterior Pituitary Powder. The activity of 0.5 mgm of the standard powder is equal to one International, U.S.P., or B.P. unit. Official pituitary preparations are adjusted to an activity of 10 units per cc of solution. No assay is made for pressor activity but this parallels oxytocic activity. Unofficial preparations are available, however, which contain the pressor principle alone. Such preparations are assayed for their pressor activity in anesthetized dogs, and one unit of pressor activity represents that exhibited by 0.5 mgm of the U.S.P., standard powdered pituitary.

Preparations and Routes of Administration. The official posterior pituitary preparations are *Posterior Pituitary,* U.S.P., and *Solution of Posterior Pituitary,* U.S.P. (*Pituitary Extract,* B.P.). The first-named drug is a dried powder containing one unit in 0.5 mgm, the solution is an extract of the powder and contains 10 units per cc. Both the oxytocic and pressor principles are contained in these preparations. *Pituitrin* (N.N.R.) is a brand of Solution of Posterior Pituitary, U.S.P. *Pitressin* (N.N.R.) contains 10 units of pressor activity and less than one-half unit of oxytocic activity per cc. *Pitocin* (N.N.R.) contains 10 units of oxytocic activity and less than one-half unit of pressor activity. Some pharmaceutical houses distinguish between so-called *"surgical"* and *"obstetrical"* solutions of posterior pituitary. The former is double the strength of the official solution; the latter is identical with the official solution.

Extracts of posterior pituitary must be administered parenterally because the active principles, being polypeptide in nature, are destroyed in the gastrointestinal tract. The usual route of administration is subcutaneous or intramuscular. The mucosal surfaces of the vagina and nose may also be employed for slow absorption and sustained action of the posterior pituitary principles.

The fate of the posterior pituitary principles is not completely known. They are inactivated by the blood and tissues, and after high doses they may be partially excreted in the urine.

Therapeutic Uses. The *oxytocic action* of posterior pituitary extract on the uterine musculature is often employed clinically. This is discussed in detail under the therapeutic uses of the oxytocics (page 668). The clinical applications of the *antidiuretic* action of extract of posterior pituitary are presented elsewhere (page 650). Posterior pituitary has been employed in a variety of conditions in which its use is not specific. It is of some value in the relief of the *intestinal paresis* and *distention* following abdominal operations or accompanying toxic febrile conditions. Five to 10 units are given by intramuscular injection. It is probably the pressor principle which is the effective agent and therefore pitressin is often used (Frazier, 1937). Relief of intestinal ileus can also be obtained from the parasympathomimetic drugs. The action of pitressin on the bowel has been utilized prior to cholecystography in order to remove obscuring flatus (Kirklin and Seedorf, 1939). Several investigators have reported that injections of pituitary extract are helpful in treating *herpes zoster*. The mechanism of action is obscure and the clinical evidence of its value is contradictory.

Attempts have been made to maintain the blood pressure in *shock* with pituitary extract. Although in shock the capillaries are dilated, more than capillary constriction is required to correct the condition and the extract is of little value. The usefulness of pituitary extract as a pressor agent in various clinical *hypotensive states* is extremely limited and the experimental data presented clearly indicate the reason for this.

Untoward Reactions and Contraindications. Following the injection of solution of posterior pituitary, marked facial pallor as a result of vasoconstriction is commonly observed. There is no rise in blood pressure, however. Increased intestinal activity is likely to cause nausea, belching, cramps and a desire to defecate. Women are apt to experience menstrual-like uterine cramps. The use of posterior pituitary solution is contraindicated in individuals suffering from vascular disease, especially disease of the coronary arteries.

THE CLINICAL USE OF OXYTOCICS

There are definite indications for and contraindications to the clinical use of the oxytocics. These may be summarized dogmatically for there is a unanimity of opinion on this subject. In brief the indications for the employment of an oxytocic drug are: (1) to induce labor at term if this should prove necessary, (2) to control postpartum hemorrhage arising from atony of the uterus, and (3) to aid and hasten the normal involution of the uterus during the puerperium. The oxytocics are contraindicated during the first and second stages of labor.

The Induction of Labor at Term. When it is necessary to induce labor at full term, it is often possible to do so by the use of drugs. There is a variety of possible procedures and often several are used in sequence starting with the least drastic measure. In many cases, a cathartic is all that is necessary to initiate uterine activity. Castor oil in 30 to 60 cc doses is often employed for this purpose. The cathartic has no direct effect upon the uterus but apparently the organ is reflexly stimulated as a result of pelvic vascular congestion and intestinal irritation. The indirect action of cathartics on the uterus is often enhanced by giving quinine. The alkaloid has the property of intensifying uterine contractions and is comparatively safe to use because its action is not sufficiently powerful to cause uterine spasm. When quinine is combined with castor oil, it is usually administered two hours after the oil. It is given hourly in doses of 0.2 gram until labor is induced or a total dose of one gram is reached. If this combination therapy fails in its objective, a posterior pituitary preparation containing the oxytocic principle may be employed. Here caution is advised because posterior pituitary extract is a powerful uterine stimulant. One should start with a very small dose which may then be gradually increased. The extract is administered parenterally, usually by intramuscular injection. The procedure recommended by Davis (1937) is to give an initial injection of 0.03 cc of solution of posterior pituitary. Injections are continued at 15-minute intervals, the dose being increased by 0.03 cc at each injection until a dose level of 0.2 cc is reached. This dose is repeated at the same intervals until a total of 1.0 cc of solution has been administered. If labor is initiated, further medication is stopped. During the entire procedure the uterus should be carefully observed and if at any time it contracts so forcibly as to interfere with the fetal heart tones, the drug should be immediately discontinued. Occasionally, even the cautious use of posterior pituitary extract will stimulate the uterus to a sustained tetanic contraction which may so interfere with the placental circulation that it may be necessary to administer a general anesthetic to effect uterine relaxation.

When employed at term, the oxytocic drugs successfully induce labor in about 50 per cent of cases. If they fail, one may resort to mechanical procedures such as puncture of the membranes, dilatation of the cervix, hydrostatic dilating bags, etc.

Premature Labor and Therapeutic Abortion. The uterus at term is very sensitive to motor stimulants. During the first and second trimesters of pregnancy, however, the uterus is resistant to the action of oxytocic drugs and it is impractical to attempt to induce labor or produce abortion with these agents. Should abortion occur spontaneously, the indications for the use of oxytocics are the same as after the delivery of a viable fetus.

First and Second Stages of Labor. *Oxytocic drugs should never be used during the first and second stages of labor.* The type of contraction which they produce is too forceful and sustained to be compatible with the safety of the mother and fetus. In normal labor, events move in an orderly and purposeful manner. Each period of uterine contraction is followed by one of relaxation. This sequence not only allows a rest period for the uterine musculature but also assures adequate placental circulation. During this period of uterine activity the cervix gradually dilates. The oxytocic drugs are occasionally used at this stage with the hope of hastening labor, but are capable of exerting great harm.

When the uterus, under the stimulus of a drug, contracts too forcibly upon an undilated and rigid cervix, the accidents which may occur are as follows: (1) the force of the contraction may drive the presenting part through the incompletely dilated cervical tissues and result in severe laceration to the mother and excessive trauma to the infant; (2) if the soft tissues are unyielding, the uterus may rupture; (3) the forceful tetanic contraction of the uterus may asphyxiate the fetus. In spite of the dangers, oxytocics continue to be employed in the early stages of labor, and certain authorities consider this practice to be one of the principal causes for the high maternal and fetal death rates in the United States. Davis (1937) summarized this abuse of oxytocics in the following cogent manner: "It can thus be concluded that the physician who wishes to serve womankind conscientiously and honestly must allow labor to take its normal course, rarely resorting to expedients which might hasten the process but which inevitably carry in their wake injury, mild or serious, and even death to mother and baby."

Third Stage of Labor and Puerperium. It is during the third stage of labor and the puerperium that the oxytocic drugs are especially useful. After delivery of the fetus, it is desirable to have the uterus contracted. This reduces greatly the incidence and extent of postpartum hemorrhage by allowing the uterine muscle mass to constrict the large blood sinuses of the evacuated organ. On the other hand, enforced uterine contraction may prevent the normal separation and delivery of the placenta. Nevertheless, some accoucheurs do employ small doses of posterior pituitary solution immediately upon the delivery of the presenting part. If excessive hemorrhage occurs, after the birth of the baby and before the delivery of the placenta, one cc of solution of posterior pituitary may be injected intramuscularly. Although there is probably no danger in administering posterior pituitary solution routinely at the beginning of the third stage of labor (Fortin, 1938), and although the stage may thereby be somewhat shortened, the usual procedure is to *await the delivery of the placenta before the administration of an oxytocic.* At the completion of labor, oxytocic drugs are used routinely by obstetricians. If there is severe postpartum hemorrhage due to uterine atony, a motor stimulant to the uterus is always indicated before more radical measures are employed. It should not be given unless the cause of the bleeding has been ascertained, for obviously an oxytocic would be useless in controlling hemorrhage resulting from a deep cervical tear or uterine rupture.

Before the introduction of ergonovine, posterior pituitary solution (1.0 cc) was usually given intramuscularly to control postpartum bleeding. It was the drug of choice because of its rapid onset of action. Often ergotamine (0.5 to 1.0 mgm) or purified injectable preparations of ergot (1.0 to 2.0 cc) were injected at the same time as the solution of posterior pituitary. By the time the effect of the posterior pituitary extract had worn off, action of the ergot would have begun and would continue for several hours. Ergonovine, due to its low toxicity, rapid onset, and sustained duration of action, can replace posterior pituitary extract as well as all other ergot preparations. The intramuscular injection of 0.2 to 0.3 mgm gives a rapid and lasting response. The drug may also be given intravenously in a dose of 0.2 mgm if immediate action is desirable (Figure 74). The advantages of ergonovine over ergotamine have been clearly demonstrated by Reich (1939) in a series of more than 1000 cases.

The oxytocic drugs are especially useful during the puerperium. In the normal individual, the period of uterine involution is eight to 10 weeks in duration, but the process is most rapid during the first 10 days. Although it has not been definitely established whether oxytocic drugs are of material benefit if involution proceeds normally, nevertheless many obstetricians use small doses of fluidextract of ergot (one to two cc three times daily) in order to lessen the possibility of bleeding and infection. However, if involution is delayed, definite help results from stimulation of the uterus by oxytocics because abnormal involution is usually associated with uterine atony. Under such conditions, ergonovine may be given orally or sublingually in doses of 0.2 to 0.4 mgm three times daily for as long a period as is necessary to accomplish the desired results. If infection develops in the postpartum uterus, there is evidence that the use of ergonovine may limit its spread. Although cases of gangrene have followed the administration of ergotamine in septic individuals, there is no report in the literature of such an accident resulting from ergonovine. Nevertheless, caution must be observed in the use of ergonovine for an extended period of time.

ERGOT AND THE ERGOT ALKALOIDS

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CHAPTER 37

ABORTIFACIENTS, UTERINE SEDATIVES, UTERINE HEMOSTATICS AND SPERMATOCIDES

ABORTIFACIENTS

There is a group of drugs undeservedly known as abortifacients. When administered in large amounts, the members of this group sometimes cause evacuation from the uterus of the products of conception, but this action is completely unreliable and should be viewed as a toxic one. The production of abortion by drugs is unsafe, unpredictable and definitely to be avoided. Nevertheless, drug-induced abortion is often attempted by the layman, and many missed abortions, septicemias and fatalities have resulted. For these reasons, the so-called abortifacient drugs deserve brief mention despite their complete lack of clinical usefulness.

Irritants. Certain irritant drugs may act as abortifacients by producing irritation of the genito-urinary tract and pelvic vascular congestion which on occasion may stimulate the uterus to abort. Most drugs of the irritant group are *volatile oils.*

Oil of Savin. This oil is obtained from the tops of *Juniperus sabina,* an evergreen growing in Europe and the Northern United States. It has been used from ancient times as an abortifacient and has caused many cases of fatal poisoning. Toxic symptoms consist of severe abdominal pains, bloody vomitus, diarrhea, hematuria, oliguria or anuria, convulsions, unconsciousness and death from collapse. Treatment consists in evacuation of the stomach, administration of demulcents, and supportive and shock therapy. Oil of savin is one of the most toxic of the volatile oils.

The other members of the group employed for producing abortion are so similar in action to oil of savin that they need only be named. They are oil of tansy, oil of pennyroyal, apiol and turpentine.

Endocrine Preparations. The use of endocrine preparations to produce abortion apparently has a physiological basis. The quiescence of the uterus and the maintenance of a suitable endometrial state during pregnancy is thought to result from the action of the luteal hormone, progesterone. The actions of the estrogenic hormones are antagonistic to those of progesterone. In experimental animals, it is possible to produce abortion by the administration of large amounts of estrins. Larger doses of drug are necessary to produce this effect as pregnancy advances. Abortion induced early in pregnancy by estrins probably results chiefly from endometrial changes which interfere with placental circulation, similar to those occurring after removal of the corpus luteum. Late in pregnancy, the estrin-induced abortion is probably the result of increased uterine motility. As yet, this action of estrins has had little clinical application.

Motor Stimulants. The oxytocic drugs previously discussed stimulate the motor activity of the uterus and are capable of producing abortion. They have little action in early pregnancy, but may cause premature delivery if large doses are given near term. Thus abortion is one of the symptoms of ergot poisoning.

UTERINE SEDATIVES OR ANTISPASMODICS

"Uterine sedatives" supposedly diminish excess muscular activity of the uterus. They are chiefly employed in dysmenorrhea. Excessive pain accompanying menstruation may

in some cases be due to tetanic uterine contractions. The hormone of the corpus luteum probably has a definite and important antispasmodic action on uterine muscle. The therapeutic use of *progesterone* as a uterine sedative is discussed elsewhere.

Extracts of *Viburnum* (*prunifolium* and *opulus*), several of which are official in the N.F., were formerly employed extensively as uterine sedatives. Pharmacological studies have failed to reveal any activity of these extracts and they are now seldom used.

UTERINE HEMOSTATICS

A group of drugs employed to control excessive uterine bleeding are known as uterine hemostatics. They are ineffective and therapeutically unimportant.

Extracts of *Hydrastis* (Golden Seal), several of which are official in the N.F., have been rather extensively employed. They contain three alkaloids, berberine, hydrastine and canadine. *Hydrastine,* N.F., is an isoquinoline derivative closely related structurally to certain opium alkaloids. Extracts of hydrastis are supposed to exert a hemostatic action indirectly through stimulation of the uterine musculature, thus compressing blood vessel The drug is seldom used and does not warrant serious consideration as a therapeutic agent.

SPERMATOCIDES

Several methods can be employed for the control of conception. One of these is the use of chemical agents designed to immobilize spermatozoa before they gain access to the uterus. The drugs used for this purpose are termed spermatocides. Unfortunately, they are prescribed almost exclusively in the form of expensive proprietary preparations of secret composition.

Properties Desired in Contraceptive Preparations. There are certain basic requirements which contraceptive preparations should possess to be of practical value.

Effectiveness. Effectiveness is obviously the most important requirement. This depends upon spermatocidal, physical and chemical properties, and ease of application. A contraceptive drug should be almost instantaneously spermatocidal in moderate dilution. Physical characteristics of the preparation should be such that it can penetrate into the rugae of the vaginal mucosa and spread over the surface of the vagina and cervix to form a protective film. These properties should persist even when the contraceptive is diluted with cervical and vaginal secretions. Chemically a contraceptive should be stable, uniform and miscible or soluble in the vaginal secretions. Naturally, ease of application is also essential.

Pharmacological Properties. A contraceptive agent must have no deleterious action on the vaginal mucous membranes. Neither should it have systemic toxicity because the vaginal mucosa offers an effective site of absorption for many drugs. Also it should retain its pharmacological action over a relatively long period of time.

Esthetic Properties. The esthetic properties of contraceptive drugs and their vehicles must also be considered. They should be, in so far as is possible, odorless, colorless and stainless. The method of application should also be reasonably convenient.

Vehicles and Contraceptive Drugs. The physical, esthetic and, in large part, the chemical properties of commonly used contraceptive preparations are mainly determined by the vehicle or base in which the spermatocidal agent is carried. The most widely used vehicles and forms of administration are *jellies, suppositories, powders, effervescent tablets* and *aqueous solutions.*

Jellies. The jellies are the most extensively employed form of administration of contraceptive drugs. A jelly base best fulfills the physical and chemical requirements outlined. The jellies used must be water-soluble and therefore such a preparation as petrolatum is useless.

Glycerite of starch is the most commonly utilized jelly base. It has the unique advantage of being in itself quite spermatocidal. However, it has certain disadvantages because it is dehydrating to tissues and quite irritating to some individuals. In its place may be substituted the vegetable gums. The most frequently employed are *gum tragacanth, gum acacia, gum karaya, chondrus crispus* (Irish moss), *gum bassora,* and *agar.* The methods of preparation of most of these bases may be found in the N.F. or U.S.P. and are quite familiar to pharmacists.

Spermatocidal Drugs Employed in Jelly Bases. There is also a wide choice of spermatocidal agents which may be incorporated in any of the aforementioned jelly bases. The cheapest, most effective and most commonly employed are acids. The motility of spermatozoa ceases at a pH less than 6.0, but unless the pH is reduced to 4.0 motility may be resumed. The acids commonly used and the percentages employed are as follows: *lactic acid,* one to two per cent; *acetic acid,* one per cent; *citric acid,* one per cent; *boric acid,* five per cent. Boric acid is only weakly spermatocidal, but it is usually incorporated in contraceptive jellies because of its mild antiseptic and preserving qualities.

Aluminum salts are commonly used in jellies as spermatocides, and are active by virtue of their ability to precipitate proteins. Potassium aluminum sulfate is the salt usually employed. Although the compound is effectively spermatocidal, it may cause drying and hardening of the mucous membranes. It is used chiefly when an astringent is desired for relaxed vaginal tissues. Because the salt is only slowly spermatocidal in concentrations of 0.25 per cent and is an active tissue astringent in the more effective concentration range of 0.5 to 1.0 per cent, it is impossible to avoid this side-action.

Paraldehyde and *paraformaldehyde* have been employed in 0.1 per cent concentration in contraceptive jellies. They are not often used because they have an injurious effect on tissues. Also, certain individuals are hypersensitive to these drugs.

Hexylresorcinol is an effective and harmless contraceptive. It is highly active when incorporated in a jelly base in 0.03 per cent concentration. The pharmacology of hexylresorcinol is discussed elsewhere.

Oxyquinoline sulfate (chinosol) has been extensively used and has gained an undeserved reputation as a spermatocide. The concentration of the drug usually employed is 0.1 per cent but even solutions as strong as three per cent are only slowly spermatocidal. If high concentrations are used, the possibility of systemic absorption of harmful amounts of the drug exists.

Quinine has also been employed as a spermatocide, but higher concentrations than are safe must be used before a reliable degree of activity is obtained.

Of all the drugs described, the acids are probably the safest and simplest, and they are reasonably effective. For example, lactic acid (two per cent) and boric acid (four per cent) may be conveniently prescribed together in glycerite of starch to make a satisfactory contraceptive jelly. Any of the drugs or jelly bases discussed may be similarly compounded. For ease of application the contraceptive jelly is usually dispensed in a collapsible tube fitted with a nozzle for insertion into the vagina. The jelly should be generously applied as near to the cervix as possible.

Suppositories. Spermatocidal drugs may also be incorporated in suppositories. *Cocoa butter* is a common suppository base and is useful because it melts at body temperature. A decided disadvantage is that cocoa butter does not allow the incorporation of solutions of the water-soluble spermatocidal drugs. Neither does it mix with vaginal secretions. Gelatin suppositories overcome these objectionable features but they do not have a sharply defined melting point. Suppositories are more expensive than jellies. Only those spermatocidal agents which are miscible with suppository bases can be employed in this manner.

Powders. Powders may be used as diluents and vehicles for spermatocidal drugs. The resultant preparations are used with a specially designed vaginal insufflator or atomizer. In order to be effective the active ingredients must dissolve in the vaginal secretions and therefore powders are not serviceable unless secretion is adequate. Only dry ingredients in a state of very fine division can be placed in powders; otherwise effective spraying is impossible. Powders do not fulfill all the requirements outlined at the beginning of this section. Those commonly used are *starch* and *gum arabic.* Drugs employed in powder vehicles are *boric acid, tannic acid, potassium aluminum sulfate, zinc salts* and *quinine.* An example of a contraceptive powder is as follows: tannic acid, four per cent; boric acid, eight per cent; gum arabic, 20 per cent; starch, 68 per cent.

Effervescent Tablets. Effervescent tablets usually contain a spermatocide incorporated with an effervescent mixture such as tartaric acid and sodium bicarbonate. Supposedly the evolution of carbon dioxide causes sufficient foam to act as a mechanical barrier to the spermatozoa and thus give the spermatocidal agent a longer period of time in which to work. *Boric acid* and *oxyquinoline sulfate* are drugs often used in this manner. Tablets vary in weight from 0.3 to 1.0 gram. They are difficult to make, deteriorate if exposed to moisture, depend upon vaginal secretions for their activity, and are seldom used.

Solutions. Simple aqueous solutions of the water-soluble spermatocidal drugs may also be employed. Their use as a douche following coitus is not to be recommended as a contraceptive procedure, for by the time the douche is usually performed the spermatozoa may be out of reach of chemical agents. Tampons made from a piece of rubber sponge may be soaked in one of these solutions and placed in the vagina in the proximity of the cervix. This is a simple, inexpensive and quite effective procedure. The concentration of drugs employed is the same as that used in the jellies. Inasmuch as the tampon method is often recommended when expense is a primary consideration, one may use household vinegar (five per cent acetic acid) diluted five times, or lemon juice (five per cent citric acid) diluted five times.

SECTION X

GASES AND VAPORS

A number of pharmacological agents have in common the property of being gaseous at ordinary temperatures and pressures. Others are liquids of very low vapor pressure which can yield vapors in sufficiently high concentration to possess pharmacological activity. The various gases and vapors have little in common except that they are absorbed chiefly by way of the respiratory tract. In other respects, they comprise a heterogeneous group of drugs and poisons and are discussed together here only for the purpose of convenience. From a pharmacological standpoint, the gases and vapors may be classified in three large groups, —*therapeutic, noxious* and *inert*. Aside from the anesthetic gases and vapors which are discussed elsewhere, the only important agents of the therapeutic group are *oxygen, carbon dioxide* and *helium*. Noxious gases and vapors are too numerous for complete discussion and space is devoted only to the more important members of the group, especially those which produce a high incidence of poisoning. As examples of toxic gases and vapors may be mentioned *carbon monoxide, hydrogen cyanide,* the *war gases,* etc. Inert gases assume toxicological importance only when they are present in amounts sufficiently high to reduce the concentration of oxygen below that normally present in the inspired air, a property which does not warrant further discussion of the group. An outstanding example of an inert gas is *nitrogen*. Although helium is correctly viewed as an inert gas, it possesses valuable therapeutic actions due to its unique physical properties, and helium is therefore included among the therapeutic gases.

CHAPTER 38

THE THERAPEUTIC GASES

OXYGEN, CARBON DIOXIDE AND HELIUM

OXYGEN

The importance of oxygen to the animal organism is obvious. Of the three basic essentials for the maintenance of life—oxygen, water and nutriments—the deprivation of oxygen leads most rapidly to death. Tissue cells must be continually supplied with oxygen by the circulation, for they have no reserve store. Often in disease or poisoning there is an interference with the normal oxygenation of the blood or tissues. Under such circumstances the administration of oxygen may be a life-saving procedure. Also oxygen has several unique applications as a therapeutic agent unassociated with the ability of the gas to support combustion.

History. Oxygen therapy was introduced by Beddoes, whose publication in 1794, in collaboration with Watt, entitled, "Considerations on the Medicinal Use and Production of Factitious Airs," might be considered the beginning of inhalation therapy. His collaborator was James Watt, engineer and inventor of the steam engine. Beddoes had established the Pneumatic Laboratory at Bristol. Here, overcome with enthusiasm for his project, he treated all kinds of diseases with oxygen. These included such varied conditions as scrofula, leprosy, and paralysis. This lack of discretion in therapeutic application naturally led to many failures and Beddoes died a disconsolate man. It is interesting to note that Beddoes' assistant was Sir Humphry Davy. When Beddoes' experiments proved disappointing, Davy left the laboratory in order to pursue his own investigations on the properties of nitrous oxide. Davy's contribution to the history of anesthesia has already been mentioned.

It was only following such pioneer investigations as those contributed by Haldane, Hill, Barcroft, L. J. Henderson and Y. Henderson that oxygen therapy was placed upon a sound physiological basis. Oxygen is now a recognized therapeutic agent, but, as in the time of Beddoes, the indiscriminate use of the gas will only bring disappointing results. One must limit the application of this agent to those conditions in which the pathological physiology of the disease being treated is of such a nature that symptoms can be relieved by the inhalation of oxygen.

Oxygen Deprivation. If the oxygen concentration in inspired air is reduced, the symptoms of anoxia ensue. These symptoms vary in intensity with the degree of oxygen reduction and the resulting effect on the oxygen content of the blood. Air normally contains 20.9 per cent of oxygen. This partial pressure in the lungs allows the hemoglobin to be approximately 95 per cent saturated with oxygen. If the concentration of oxygen in the air is reduced to from 12 to 16 per cent, the arterial blood is then only 85 to 89 per cent saturated. Even this slight reduction in saturation will lead to definite symptoms of anoxia. These include accelerated pulse and respiration, a decreased ability for mental concentration and a loss of finer muscular coordination. If the oxygen content of the inspired air is as low as from nine to 14 per cent, the arterial blood is only 74 to 87 per cent saturated. Under such circumstances, the tissue supply of oxygen is so reduced as to lead to numerous symptoms. Many of these are referable to the central nervous system, for brain tissue is most sensitive to oxygen deficit. Judgment is faulty, emotions are very labile and easily aroused, fainting is quite common, analgesia is present, muscular function is impaired, the gait is staggering, and muscular effort results in quick fatigue. If the oxygen saturation of the blood is reduced below 74 per cent, which results from continued breathing of an atmosphere containing less than 10 per cent of oxygen, an individual becomes unconscious due to the loss of function of cortical cells. Continued anoxia leads to a progressive descending depression of the central nervous system and finally medullary failure occurs with cessation of respiration. The heart continues to beat for a short time after the respiration has failed.

Anoxemia is accompanied by circulatory changes. Blood pressure and cardiac output are increased reflexly from stimulation of the carotid body by the anoxemia. Reflex respiratory stimulation also results from the effect of anoxemia on the carotid body (Comroe and Schmidt, 1938), and is evidenced chiefly by an increase in the rate of respiration, depth being only slightly affected. In the terminal stages, however, the medulla may be directly stimulated by anoxia before depression occurs.

The symptoms of anoxia can be almost immediately relieved by the administration of oxygen. However, if cells are deprived of oxygen over an extended period of time, they may fail to regain their function when oxygen is restored. The cells most susceptible are those of the central nervous system and the higher centers are more vulnerable to anoxia than are the lower. Thus cortical cells may not regain their function after they have been deprived of oxygen for as little as five minutes whereas 30 minutes of anoxia are sometimes necessary before the medulla is irreversibly damaged. It follows therefore that severe anoxia may result in permanent damage to the central nervous system. Cases have been reported in which all the signs of decortication have accompanied recovery from an extended period of respiratory failure.

Oxygen Excess. When high concentrations of oxygen are breathed, the composition of the blood is changed little. Ordinarily, hemoglobin is 96 per cent saturated with oxygen and carries 19.2 cc of this gas per 100 cc of blood. Increasing the partial pressure of oxygen in the alveolar air can only raise this amount to 20.0 cc of oxygen per 100 cc of blood. In addition to the oxygen carried by hemoglobin, there is some in simple solution in the plasma. Under ordinary conditions, only about 0.3 cc per 100 cc of blood is present in the plasma, but if pure oxygen is breathed the amount of the gas in solution is increased to 2.2 cc per 100 cc of blood. Thus, the amount of oxygen in the arterial blood can be increased by approximately 15 per cent by the inhalation of pure oxygen. This increase has no effect on tissue function under normal conditions but in clinical conditions, characterized by oxygen want, this 15 per cent increase can often be beneficial (Boothby, Mayo and Lovelace, 1939). In this connection, Campbell and Poulton (1934) demonstrated that the oxygen pressure in tissue is increased proportionately more than the increase in oxygen content of the blood.

The effect of high concentrations of oxygen on the epithelium of the lung, the one tissue exposed to a marked increase in oxygen pressure, is a subject of controversy. Numerous investigators have reported that the inhalation of oxygen in concentrations exceeding 80 per cent for 24 to 48 hours results in a typical local response in the lungs which consists of congestion, edema, and finally a fibrinous bronchopneumonia. Smith, Bennett, Heim, Thompson and Drinker (1932) investigated the effect on rats of an atmospheric pressure of 3040 mm of mercury (4 atmospheres), the partial pressure of oxygen being 635 mm of mercury or equivalent to 83.6 per cent oxygen at normal barometric pressure. Despite the high total atmospheric pressure, the harmful factor in this environment was attributed to the increased oxygen tension. Symptoms designated as acute oxygen poisoning, consisting of hyperemia and edema of the lungs, developed on the fourth day; 13 per cent of the animals succumbed. Exposure was continued in the remainder for 72 days and the only untoward symptom noted was weight loss. Tolerance to the high oxygen tension evidently developed, which the investigators attributed to the hyperplasia and hypertrophy occurring in the pulmonary alveoli. These morphological changes persisted for months after exposure. In contrast to the experimental results obtained in rats under high atmospheric pressure are the clinical observations of Boothby (1938) and Boothby, Mayo and Lovelace (1939). These investigators administered oxygen continuously in 90 to 100 per cent concentration to approximately 800 patients for periods of as long as 48 hours without any evidence of pulmonary irritation. Nevertheless, they warn that longer periods of administration of this high concentration should not be used for the present. For the most part, however, when oxygen is administered as a therapeutic agent, the concentration of the gas in the inhaled mixture is limited to from 40 to 60 per cent. There is a growing conviction among clinicians, however, that even pure oxygen may not be deleterious to the human lung and that when high concentrations are necessary to produce the desired effect, they should be used.

Preparations. Oxygen is a colorless, odorless and tasteless gas. Official U.S.P. and B.P. preparations are of specified purity. Oxygen is marketed in a compressed form in steel cylinders. The cylinders are fitted with reducing valves for delivery of the gas.

Methods of Administration. The various methods for the administration of oxygen can only be briefly mentioned here.

Oxygen tents are commonly used. They consist of light portable tent-like structures made from various types of fabrics. They fit over the patient's head and thorax in a fairly air-tight manner. It is necessary to cool the air within the tent and to absorb the accumulating carbon dioxide. The concentration of oxygen within the tent depends upon the efficiency of the particular apparatus employed and the rate at which the gas is delivered. Obviously, the most efficient tent is one that maintains a high oxygen content with a minimum rate of flow. There are several reliable types on the market. Oxygen tents are desirable for they are fairly comfortable and permit administration of any desired concentration of oxygen over long periods of time.

A simple method for the administration of oxygen is by means of a *nasal catheter*. In this procedure, a soft rubber catheter is inserted into the nasopharynx through the nostril. Care should be exercised so that the tube does not enter the esophagus. Oxygen is then passed through the tube and the rate of flow determines the concentration which enters the alveoli. A flow of about two liters per minute increases the oxygen tension in the alveoli to a little over 30 volumes per cent. If a flow of four liters per minute is maintained, the oxygen tension of the inspired air is more than double that normally breathed. If a double nasal catheter is used, 50 per cent oxygen can be introduced into the lungs.

Another simple method for the administration of oxygen, which is more effective than a nasal catheter, is a simple *face mask*. These masks are usually equipped with a valve which permits expiration and an opening to the outside which allows for dilution of the oxygen. If this opening is completely closed, it is possible to administer 100 per cent oxygen with this apparatus. It is economical and efficient, but unfortunately patients object to having the mask pressed against the face for long periods of time. Boothby (1938), Lovelace (1938) and Bulbulian (1938) have described oxygen masks of a nasal or oronasal type (B.L.B. inhalation apparatus). These masks are inexpensive to purchase and maintain, supply oxygen efficiently and in any desired concentration, and are comfortable for the patient. Furthermore, mechanical simplicity and ease of operation permit their use in smaller hospitals, by the family physician in the patient's home, and by aviators and aeroplane passengers. (Also *see* Boothby, Mayo and Lovelace, 1939.)

Oxygen has also been given by intravenous and subcutaneous injection. It is extremely doubtful whether a sufficient quantity of the gas can be absorbed following subcutaneous administration to be of much practical value. In experimental animals, it is possible to prolong life for several hours by the intravenous administration of oxygen after respiration has ceased. Clinically, however, this procedure is dangerous in that gas emboli may occur from too rapid an injection. Although sporadic reports have appeared claiming good results, this technic is not recommended and cannot be compared with the inhalation of oxygen.

Therapeutic Uses. Oxygen is used mainly to overcome the symptoms of anoxia. However, even in the treatment of anoxia it may be of limited value.

Physiological Considerations. Various types of anoxia have been recognized (Barcroft, 1920; Peters and Van Slyke, 1931). The following classification is taken largely from that of Peters and Van Slyke:

1. *Anoxic anoxia.* This condition is characterized by a low arterial oxygen tension. In most cases the oxygen capacity of the blood is normal but the hemoglobin is not carrying the gas to the limit of its capability. The most frequent cause of anoxic anoxia is a mechanical hindrance in the lungs which prevents the free diffusion of gases from the alveoli into the blood. This may arise from pulmonary edema, consolidation, atelectasis, fibrosis, emphysema or bronchospasm. Other conditions may give rise to a low oxygen tension in arterial blood. Among them are shallow breathing, a low oxygen tension in the respired air, and a flow of blood from the right to the left heart through a perforate cardiac septum or patent ductus arteriosus.
2. *Anemic anoxia.* This condition arises when the amount of hemoglobin available for the carriage of oxygen is reduced. The common causes are the anemias, methemoglobinemia, sulfhemoglobinemia and carbon monoxide poisoning.
3. *Stagnant anoxia.* In this condition the tissues do not receive sufficient oxygen because their circulation is inadequate. The three most prominent predisposing causes are lowered arterial blood pressure arising from shock, hemorrhage, etc., increased venous pressure resulting from cardiac failure or venous obstruction, and local circulatory insufficiency from constricted or diseased blood vessels.
4. *Histotoxic anoxia.* In this condition, plenty of oxygen is available for the tissues but the cells are unable to utilize it because they have been poisoned. The outstanding agent which interferes with cellular respiration is the cyanide ion. Alcohol and certain narcotics may also interfere with the tissue uptake of oxygen.

It should be obvious that the administration of oxygen by inhalation can be of value only in certain of the above conditions. In general, it may be stated that oxygen therapy is of greatest benefit in acute and severe forms of oxygen want when anoxia arises from inadequate oxygenation of the blood passing through the lungs. Therefore, with few exceptions, the therapeutic usefulness of oxygen is in anoxic anoxia. For example, in shock, the circulation is inadequate and the tissues are not receiving sufficient oxygen. However, that blood which is slowly passing through the lungs is being saturated with oxygen to a normal degree. Increasing the oxygèn tension in the inspired air can do no more than raise the oxygen content in the blood by a few per cent, an amount insufficient to compensate for an inadequate circulation. Likewise, in severe anemia, the blood is carrying oxygen almost to the limit of its capabilities and little can be gained from oxygen administration. In an individual poisoned with cyanide, not only is the arterial blood saturated with oxygen but the oxygen tension in the venous blood is far above normal for the reason that the tissues cannot extract their normal quota of this gas. Oxygen therapy in such a case would be useless. On the other hand, when the lungs are filled with exudate so that there is a mechanical barrier to the diffusion of oxygen, the arterial blood is unable to obtain sufficient oxygen from the inspired air despite the fact that it is capable of carrying a normal amount. The administration of oxygen almost immediately raises the oxygen tension of the arterial blood to a normal level and the relief of symptoms is dramatic.

Those clinical conditions in which oxygen has been found to afford relief may now be discussed.

Pneumonia. Oxygen is of great value in the treatment of both lobar and bronchopneumonia. Stadie (1919) made a complete study of the oxygenation of the blood in cases of pneumonia and his findings elucidate the physiological basis for the use of oxygen in this condition. Stadie demonstrated that the symptoms of anoxia in pneumonia resulted from the inability of the venous blood to become oxygenated in the lungs. Therefore this condition can be classified as a true anoxic anoxia. Oxygen unsaturation of over 20 per cent in the arterial blood, Stadie found, was usually associated with a fatal outcome of the disease. At the same time, he demonstrated the improvement in the oxygen saturation of the blood which follows inhalation of 40 per cent oxygen mixtures. In pneumonia it is probable that several factors combine to prevent the oxygen in the lungs from reaching the blood. In the first place, there is the physical obstruction caused by edema, exudate, and changes in the bronchial epithelium. These form a mechanical barrier between the inhaled gas and the circulation. Secondly, in certain types of pneumonia, large areas of the lung may be consolidated. The circulation to these areas is greatly reduced. If cardiac output remains unchanged, the rate of blood flow through the remainder of the pulmonary vascular bed must be considerably speeded. This reduces the time available for the process of oxygenation. Lastly, pneumonia may be characterized by tachypnea. This type of rapid shallow breathing, even when unassociated with pathological changes in the alveoli, is conducive to anoxia.

The administration of oxygen compensates for these abnormalities. At higher partial pressures, more oxygen can penetrate the mechanical obstruction. Also, the increased oxygen tension permits adequate oxygenation despite the increased rate of pulmonary blood flow. As the degree of anoxemia is reduced, the tachypnea is relieved. The optimal concentration of oxygen for the treatment of pneumonia is between 40 and 60 per cent. The purpose of the therapy, however, is to overcome anoxia and if this is not accomplished quickly, the concentration should be further increased.

Obviously, oxygen does not attack the basic cause of the disease. Improvement is purely symptomatic. However, oxygen therapy increases the oxygen saturation of the blood and relieves cyanosis. It gives great comfort to the patient and eases the breathing. The pulse and respiration, which are usually increased in response to the anoxia, are slowed and often there is a marked drop in temperature. These factors combine to prolong life and increase the patient's strength until the body's immunity is sufficiently developed successfully to cope with the disease or until chemotherapy exerts benefit.

Many believe that oxygen therapy in pneumonia should be prophylactic in nature and advise that it be started immediately after the disease is diagnosed. Others wait for definite symptoms of anoxia to develop, the chief indications for oxygen being either a persistent tachycardia of more than 120 beats per minute, a respiratory rate of more than 35 per minute, cyanosis or delirium. There is some evidence that the early use of oxygen may exert a favorable influence on the course of the disease. Once anoxia develops, there is no doubt that oxygen administration should be a major feature of therapy.

Other Lung Disorders. Oxygen therapy is not limited to pneumonia. There is a variety of other pathological changes in the lungs which interfere with normal oxygenation. In *pulmonary edema,* the administration of oxygen is effective in maintaining a normal concentration of oxygen in the circulation. Likewise, the gas is effective in acute severe exacerbations of bronchitis, emphysema and bronchiectasis. Oxygen has also been employed for the relief of severe asthma, but in this condition, where access of gas to the alveoli is prevented by a constriction of the airways, the use of helium is more effective.

Circulatory Diseases. Oxygen is useful in certain types of circulatory disorders. Its application should be limited to conditions associated with pathological changes in the lungs. Harrop (1919) showed that in *cardiac decompensation,* the oxygen saturation of the blood may be reduced by 10 to 15 per cent. This is partially the result of pulmonary edema which arises from vascular stasis and prevents normal oxygenation. In addition, there is also a stagnant anoxia associated with cardiac insufficiency. Oxygen therapy results in the relief of cyanosis and a slowing of the pulse. It should be obvious, however, that treatment should be directed primarily toward improving cardiac function. The value of oxygen is to afford temporary relief from distressing symptoms.

Barach and Levy (1934) pointed out the value of oxygen therapy in *acute coronary occlusion*. They postulate the following sequence of events to establish the rationale of therapy. Following coronary occlusion, a portion of the myocardium is deprived of blood, and as a result there is impaired cardiac function. If a sufficiently large area is involved, cardiac output is diminished and passive congestion may occur and lead to pulmonary edema. This in turn results in poor absorption of oxygen and incomplete aeration of the blood in the lungs. As a consequence, the degree of cardiac anoxia is increased and a vicious circle has been established. Barach and Levy recommend that in the event of coronary occlusion, oxygen therapy should be started at the first indication of cardiorespiratory impairment. Following such therapy, they have observed that (1) the patient shows subjective improvement with striking relief of pain, slower and less labored respiration and diminished restlessness; (2) cyanosis is diminished or abolished; (3) Cheyne-Stokes respiration, if present, is relieved; (4) the temperature, if elevated, falls; and (5) the heart rate is slowed, the beat is strengthened, and pulmonary congestion is relieved. Proof that the oxygen therapy is directly concerned with the relief of this syndrome is obtainable by withdrawing the gas, whereupon there is a return of symptoms. Lovelace (1938) and Boland (1940) have also reported favorably on the relief of the symptoms of coronary thrombosis by oxygen therapy. A high concentration (80 to 100 per cent) should be employed.

Attacks of *paroxysmal dyspnea* may be greatly benefited by the administration of oxygen. These attacks are frequently due to edema of the lungs resulting from pulmonary vascular stasis arising from left ventricular weakness. Morphine is commonly used in the treatment of this condition. Campbell and Poulton (1934) point out, however, that this drug will increase the degree of anoxia due to its effect on respiratory volume, and they therefore consider oxygen therapy more beneficial.

Carbon Monoxide Poisoning. The administration of oxygen is of great importance in the treatment of carbon monoxide poisoning. This is the one instance in which oxygen is effective in anemic anoxia. It is beneficial because of the fact that the conversion of carboxyhemoglobin to oxyhemoglobin is accelerated. In addition, the breathing of pure oxygen leads to an appreciable transport of this gas in physical solution in the plasma and in this manner tissue anoxia is partially relieved. Oxygen is used in high concentration usually in combination with carbon dioxide (page 697).

Miscellaneous Uses. Local oxygen therapy has been tried in the treatment of peripheral vascular disease. For example, in the ulcerative or gangrenous phase of Raynaud's disease, the afflicted area has been directly bathed with oxygen by introducing the gas into an air-tight cuff surrounding the tissue to be treated. It is known that oxygen can be absorbed to some extent by the skin and it is believed that this procedure can introduce the gas into tissues deprived of it by an inadequate circulation. Starr (1934) has reported some success with this type of therapy in that after the local application of oxygen in concentrations of over 80 per cent there is decreased cyanosis of the anoxic tissue. This therapy has not become established and more favorable results have been reported from drugs which act by producing vasodilatation, or from mechanical devices which provide passive vascular exercise or intermittent venous obstruction.

An interesting therapeutic application of oxygen is in the treatment of *chronic ulcerative colitis* (Felsen, 1931). This disease is associated with the presence in the colon of large numbers of anaerobic bacteria. Treatment consists of the introduction of the gas directly into the colon by rectal tube in the belief that the high oxygen tension will be detrimental to the anaerobic organisms. The therapeutic procedure consists in the administration of 250 cc of warmed gas every second hour. It is interesting that Fry and Dack (1936) observed that, whereas *Bacillus necrophorum* was recoverable 12 hours after its introduction into the isolated colon of a dog, the administration of oxygen made the recovery of this organism impossible.

A unique use of oxygen, in which advantage is taken of the law of diffusion of gases, is in the treatment of *abdominal distention.* This procedure was introduced by Fine and coworkers (1936; 1938) and favorable results have been reported by Lovelace (1938) and Congdon and Burgess (1939). In gaseous distention resulting from such conditions as intestinal obstruction, paralytic ileus or postoperative distention of unknown etiology, the gas which accumulates in the bowel is largely composed of nitrogen. The blood can pick up very little of this nitrogen for it has already been exposed in the lungs to air containing 79 per cent of nitrogen. If, however, 100 per cent oxygen is breathed and the partial pressure of nitrogen in the alveoli falls toward zero, nitrogen diffuses out of the blood into the exhaled air. As the nitrogen content of the blood falls, the gas in the intestine diffuses into the circulation and is excreted by the lungs. In this manner, it is possible to deflate the intestines prior to operation for obstruction or to offer relief in postoperative distention. Subcutaneous emphysema can be reduced by the same technic.

The symptoms following *pneumoencephalography,* consisting of nausea, vomiting and severe headache, can also be relieved by the inhalation of 100 per cent oxygen. The nitrogen which remains in the subarachnoid space and ventricles following the injection of air can be rapidly removed, the mechanism of action being analogous to that described. According to Lovelace (1938), the severest phase of the headache is relieved within 30 minutes after oxygen inhalation is started and in the majority of instances the headache completely disappears within four to eight hours. Oxygen has also been reported to be of value in the relief of *migraine* (Alvarez, 1939).

Oxygen has proved of value in the treatment of infections produced by certain anaerobic bacilli, especially *gas gangrene* and *tetanus.* Anaerobic organisms exposed to the unfavorable environment of oxygen become less pathogenic. Oxygen has a dual action against anaerobic gas-forming organisms. Tissues distended by nitrogen produced by such bacilli can be decompressed by the breathing of pure oxygen. This in turn permits an improved circulation to the infected area, and at the same time the oxygen content of the tissues will be at a maximum.

Schnedorf and coworkers (1940) have presented experimental evidence supporting the rationale for the use of oxygen in the treatment of *head injuries.* They observed both in patients and experimental animals that accompanying cerebral concussions with or without skull fracture the oxygen content of the arterial blood may be reduced from five to over 40 per cent. Oxygen therapy relieved the anoxemia.

CARBON DIOXIDE

The physiological rôle of carbon dioxide has long been appreciated. The gas is of paramount importance in the control of both the respiration and circulation. Normally the tension of carbon dioxide in the fluids of the body is maintained within narrow limits. Physiological maladjustments, however, can lead to a marked disturbance in the carbon dioxide content of the blood. Under special circumstances, it may be desirable to raise the concentration of this gas in the body above normal. When this is true, carbon dioxide is often of great value as a drug, and possesses unique actions which are shared by no other pharmacological agent. The status of carbon dioxide as a therapeutic agent has been reviewed by the Council (Report of the Council, 1940).

Chemistry and Preparations. Carbon dioxide is formed from the oxidation of carbon. It is an odorless and colorless gas, approximately 1.5 times as dense as air. At low temperatures it solidifies (dry ice, CO_2 snow) and the sublimation point is approximately −78 C. Carbon dioxide is marketed either in the solid form or as a gas compressed in metallic cylinders. *Carbon Dioxide,* U.S.P., B.P., is of a specified purity. For medicinal purposes, carbon dioxide is usually administered in combination with oxygen, and cylinders containing the two gases in varying proportions are available.

Pharmacological Actions

Local Actions. Supersaturated solutions of carbon dioxide in water (carbonated water, soda water) are widely employed for their local action. Such preparations are slightly acid to the taste, produce a prickling sensation of the oral mucous membranes, and are mildly rubefacient to the gastro-intestinal mucosa. This is said to increase gastric secretion and aid absorption, but the action is in all probability negligible. However, most individuals interpret the sensory effects of carbon dioxide in the mouth and throat as pleasant, and carbonated beverages and effervescent medicinals are therefore widely consumed. Supersaturated solutions of carbon dioxide also exert a mild rubefacient action on the skin. Extravagant claims have been made for the therapeutic benefits supposedly derived from bathing in carbonated waters, and various spas have prospered accordingly. Any relief of symptoms is probably attributable to the restful environment, controlled diet and psychic effect of a well-managed health resort rather than to the dubious action of the waters used for drinking or bathing.

Carbon dioxide snow is occasionally used locally as a cauterant or as a local anesthetic. It acts solely because of its low temperature, destroying or anesthetizing tissue by freezing, and has been employed for the treatment of warts, lupus erythematosus, blastomycosis, port-wine birth marks, etc.

Systemic Actions. The systemic actions of carbon dioxide which are of clinical importance are those on the respiration and circulation.

Respiration. Carbon dioxide functions in the physiological control of respiration and is one of the most valuable drugs for stimulating the respiratory center. Whether carbon dioxide is a specific respiratory stimulant or acts only by increasing the acidity of the respiratory center is a subject of debate. Although most physiologists embrace the latter view, there is no complete unanimity of opinion (Gesell, 1939). The chief site of the respiratory action of carbon dioxide is directly upon the respiratory center. However, there is evidence that an increase in the acidity of the blood flowing through the carotid body also increases respiratory exchange and it appears that stimuli from the carotid body reenforce the direct effect of carbon dioxide on the respiratory center.

The inhalation of carbon dioxide increases both the rate and depth of respiration. The intensity of its action depends mainly upon two factors. The first is the concentration of carbon dioxide in the blood, which is determined by the composition of the alveolar air. The second is the responsiveness of the respiratory center. If the center is greatly depressed, as for example by morphine, the response to carbon dioxide is minimal. The normal respiratory center is extremely sensitive, however, to changes in the tension of the gas in the blood. An increase in the tension of carbon dioxide in the alveolar air of as little as 1.5 mm of mercury above normal is sufficient to double the respiratory minute volume. Normally the partial pressure of carbon dioxide in the alveolar air is approximately 40 mm of mercury (5.2 volumes per cent). However, the inhalation of concentrations of carbon dioxide much lower than 5.2 volumes per cent is sufficient to stimulate the sensitive respiratory center. The reason for this is that normally the inhaled air contains a negligible amount of the gas, and therefore as little as 1.5 volumes per cent of carbon dioxide in the inspired air interferes with the normal excretion of the gas and increases its alveolar concentration. The relation between the concentration of carbon dioxide in the inspired air and the respiratory minute volume in normal individuals is shown in Figure 78.

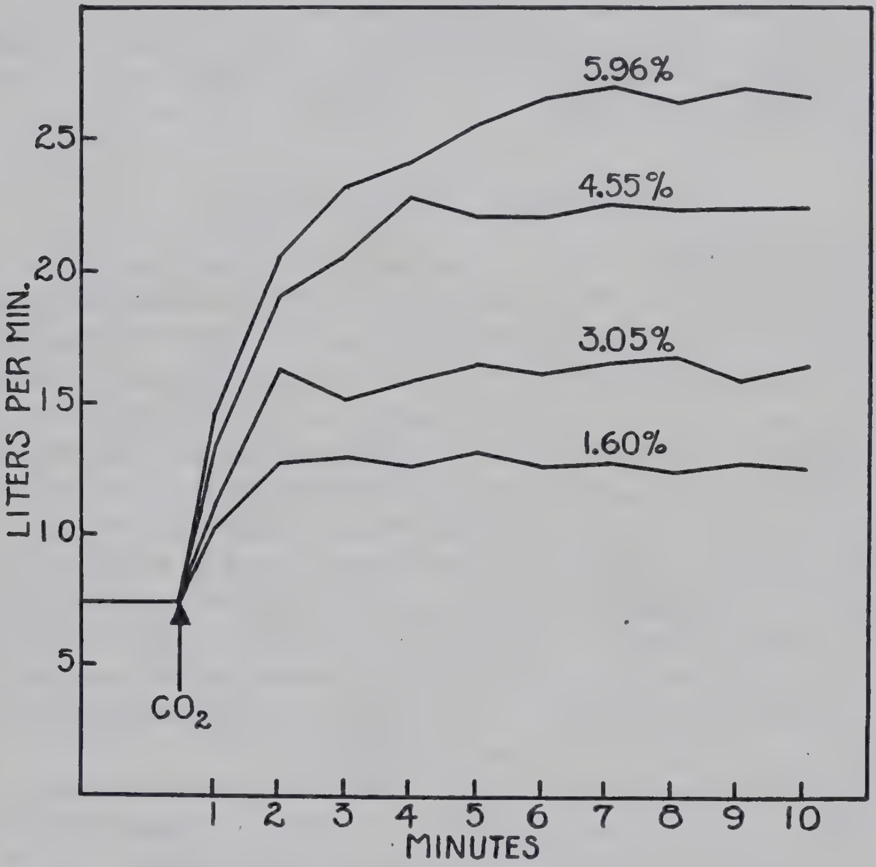

FIGURE 78. *The effect of the inhalation of varying concentrations of carbon dioxide on the respiratory minute volume of normal human subjects.* (After Padget, 1928. Courtesy of the *American Journal of Physiology.*)

In clinical practice, carbon dioxide is usually employed to stimulate a depressed respiratory center. Therefore concentrations of 5.0, 7.5, or even 10 per cent are employed. In normal individuals, the hyperpnea and discomfort occasioned by the inhalation of 10 per cent carbon dioxide for more than a few minutes would be unbearable. The breathing of 25 per cent carbon dioxide leads to unconsciousness, probably as the result of a severe acidosis, and there is only a transient hyperpnea, soon followed by muscle twitchings and clonic convulsions, coma, respiratory depression and death from respiratory failure. The breathing of pure carbon dioxide rapidly leads to death as a result of asphyxia and acidosis.

Circulation. Carbon dioxide acts both centrally and peripherally on the circulatory system. The pH of the tissues is an important factor in the control of the circulation locally, and increased metabolic activity with an associated augmentation in the production of carbon dioxide causes local vasodilatation. The central action of carbon dioxide, however, is to stimulate the vasomotor center and cause vasoconstriction. When the production of carbon dioxide is augmented by increased metabolic activity, the excess gas is excreted by the lungs and the medullary centers are not exposed to high concentrations. Thus the peripheral effects on the circulation predominate. When carbon dioxide is inhaled, however, the gas is immediately carried to the brain in high concentration and the central vasomotor stimulation which results takes precedence over the peripheral action on blood vessels. Thus peripheral blood flow is decreased and the systemic blood pressure rises (Lennox and Gibbs, 1932; Gellhorn and Steck, 1938). At the same time, however, the blood flow through the brain is increased (Lennox and Gibbs, 1932; Cobb and Fremont-Smith, 1931; Gibbs, Gibbs and Lennox, 1935) (Figure 79). This fortuitous circumstance is probably due to a direct action of carbon dioxide on the cerebral vessels which respond by dilatation to high concentrations of the gas in the brain rather than to impulses from the vasomotor center. Cerebral vasodilatation adds greatly to the value of carbon dioxide as a respiratory stimulant in that the supply of blood to the vital centers is augmented. It has also

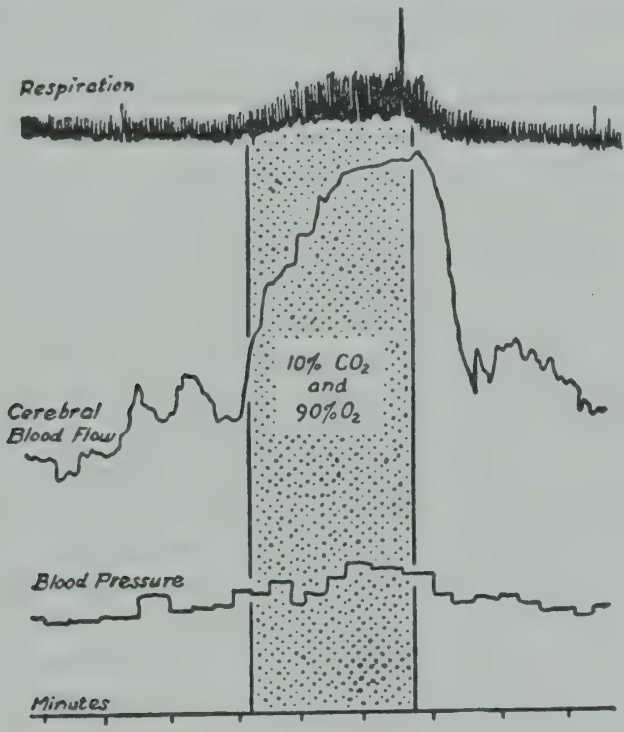

FIGURE 79. *The effect of breathing carbon dioxide on the cerebral blood flow of unanesthetized human subjects.*

A thermo-electric blood flow recorder was introduced into the internal jugular vein close to its exit from the skull. The inhalation of 10 per cent carbon dioxide in oxygen caused a prompt and marked increase in cerebral blood flow which was maintained as long as the inhalation continued. This is probably due to dilatation of the cerebral vascular bed. Note that the rate and depth of respiration were increased and that a slight rise in systolic blood pressure occurred. (After Gibbs, Gibbs and Lennox, 1935. Courtesy of the *American Journal of Physiology*.)

been claimed that the inhalation of carbon dioxide increases the tone of skeletal muscles and this in turn benefits the circulation by enhancing the venous return to the heart (Henderson and coworkers, 1936).

An increased tension of carbon dioxide in the blood also affects the heart. The distensibility of the myocardium is increased and there is a greater cardiac filling and output. Both the sinoauricular node and auriculoventricular conduction are somewhat depressed and the heart rate is slowed. If acidosis is severe, complete heart block may occur. The salutary effects of carbon dioxide on the circulation have been aptly demonstrated by Gellhorn (1937) who showed that in human beings the circulatory collapse which attends the breathing of air containing only 8.5 per cent oxygen can be prevented if three per cent carbon dioxide is added to the breathing mixture. In the same experiments Gellhorn pointed out that the symptoms of anoxia, which occur when subjects in the upright position breathe only 8.5 per cent oxygen, are prevented by carbon dioxide because of the actions of the latter gas in increasing the respiratory volume, venous return and cerebral blood flow, in stimulating the vasomotor center and in shifting the oxygen dissociation curve so that the supply of oxygen to the tissues is augmented.

Carbon Dioxide Deficiency (Acapnia). A lowered tension of carbon dioxide in the blood with a resulting alkalosis leads to the cessation of respiration. The effects of excessive carbon dioxide on the circulation are reversed. The tone of capillaries and veins is decreased; venous pressure falls; cardiac output is diminished; the period of diastole becomes shorter; rate of conduction is increased; the heart beats faster and, if alkalosis is severe, the heart may go into rigor.

The most common clinical cause of acapnia is hyperventilation. Usually when respiration stops as a result of overbreathing, carbon dioxide soon accumulates as the result of the apnea and breathing is spontaneously resumed. However, in asphyxial hyperpnea as, for example, that induced by carbon monoxide poisoning, a much more insidious condition arises. In asphyxia, the lack of oxygen stimulates overbreathing. As a result carbon dioxide is blown off through the lungs and the CO_2 tension of the blood falls. At the same time the respiratory center becomes more and more depressed because of the lack of oxygen. This factor combines with the decreased CO_2 tension to stop breathing. Spontaneous respiration cannot be restored by the administration of oxygen alone, but rather by the breathing of oxygen containing five per cent or more of carbon dioxide. Herein lies the chief value of carbon dioxide in the resuscitation of asphyxiated individuals.

Methods of Administration. Carbon dioxide is most conveniently administered by a tight-fitting mask, the gas being obtained from a storage tank. In the treatment of asphyxia, mixtures of carbon dioxide and oxygen are invariably employed. The percentage of carbon dioxide may range from five to ten, the remainder of the mixture being oxygen. It may be necessary first to introduce the carbon dioxide into the lungs by artificial respiration or tracheal catheter. For increasing the depth of respiration in conditions other than asphyxia, the gas is usually given mixed with air. This is done by means of a mask with an opening allowing the entrance of air with each respiration. A flow of carbon dioxide is then introduced into the mask, and the rate of flow determines the concentration inhaled. Roth (1937) described a technic in which carbon dioxide may be administered to a patient in an oxygen tent using CO_2 snow as a source of the gas.

Nasal and oronasal masks as described under oxygen therapy may also be employed for the administration of carbon dioxide.

Therapeutic Uses. The more important therapeutic uses of carbon dioxide gas are: (1) to stimulate a failing respiratory center, (2) to increase the volume of tidal air in order to hasten the excretion of toxic gases and vapors, and (3) to cause the lungs to expand to a maximum as, for example, in order to prevent impending atelectasis. The concentrations employed vary from five to 10 per cent.

Asphyxia. Carbon dioxide is the most valuable respiratory stimulant for initiating respiration which has failed because of asphyxia. As was mentioned previously, hyperpnea attending asphyxia reduces the carbon dioxide tension of the blood to a level below the threshold of sensitivity of the depressed respiratory center. Despite the fact that the mechanisms in the brain stem and carotid body which regulate respiration are sensitive to anoxia as well as to changes in carbon dioxide tension, the stimuli arising from anoxia soon fail to act upon the respiratory center which has become relatively insensitive because of asphyxiation. As is so aptly expressed by Gesell (1939), "One of nature's gross errors, assuming that mistakes occur in physico-chemical systems, was her concentration on the response to oxidative carbon dioxide in combating oxygen shortage, combined with her neglect of the response to oxygen lack. This error appears attributable to the depressing effect of oxygen lack which stands in the way of a more rounded control of respiration."

A combination of carbon dioxide and high concentrations of oxygen effectively combat asphyxia. The carbon dioxide provides the stimulus for the initiation of spontaneous respiration and the oxygen in high concentration soon overcomes the symptoms of anoxia. Carbon dioxide is of value in the treatment of *asphyxiation* of all types. It is of special advantage in the treatment of *carbon monoxide poisoning* in that it also hastens the dissociation of carboxyhemoglobin (page 698). The gas is of great value in the treatment of certain forms of *asphyxia neonatorum.* It not only initiates spontaneous respiration, but also helps in fully expanding the lungs if it is given intermittently during the first few days of life.

Carbon dioxide is extensively employed during and after *anesthesia.* It is effective in combating respiratory arrest due to hyperventilation or excessive depression of the respiratory center. At the conclusion of anesthesia the administration of carbon dioxide results in an increased respiratory minute volume. This hastens the excretion of anesthetic gases and vapors and reduces the time of the recovery period from anesthesia. The effect of carbon dioxide is appreciable after ether anesthesia but is little needed following the anesthesia from such agents as nitrous oxide, ethylene, cyclopropane and divinyl ether, spontaneous recovery being very rapid (Figure 7).

On some surgical services, the administration of carbon dioxide intermittently for a few days following major operations is routinely practiced. The purpose is to reduce the incidence of *postoperative pulmonary complications* which are believed by some to be caused by shallow breathing. The value of the prophylactic use of carbon dioxide cannot be stated with certainty. Some reports are extremely favorable whereas others conclude that the gas has little influence on the incidence of postoperative pulmonary complications.

Carbon dioxide has been used in the treatment of pneumonia, the purpose again being to expand the lungs to a maximum and thus promote drainage and prevent atelectasis. Favorable results have been reported in that mortality and the duration of fever are said to be reduced (Gunther and Blond, 1937). This work requires confirmation. The gas has also been successfully employed in relieving persistent *hiccup*.

Contraindications. The contraindications to the use of carbon dioxide are relative rather than absolute. Thus, whenever the gas is employed, the period of administration should be of limited duration. When concentrations of five per cent are administered for periods over one-half hour, the signs of intoxication should be looked for. A patient receiving 10 per cent carbon dioxide should be kept under constant surveillance, for signs of toxicity may appear after from 10 to 15 minutes. Toxic symptoms include unbearable dyspnea, vomiting, disorientation and a markedly elevated systolic blood pressure. The administration of the gas should be discontinued when these appear. When the systolic blood pressure reaches 200 mm of mercury, convulsions or cardiac collapse may occur. In general, it is best to stop the administration of carbon dioxide as soon as the desired effect on the respiration has been obtained or, if a lasting effect is desired, to reduce the concentration to the lowest which is compatible with the respiratory minute volume desired.

Carbon dioxide should be used with caution in the presence of respiratory obstruction. The increased respiratory effort induced by the gas may cause pulmonary edema as a result of the effects of hyperpnea and respiratory obstruction on the negative pressure within the thorax (page 691). For the same reason pulmonary edema enjoins caution in the use of carbon dioxide and only low concentrations (below five per cent) should be employed in the presence of this complication.

HELIUM

Helium is an inert gas which owes its pharmacological actions exclusively to its physical properties. It is very light and a mixture of 80 per cent helium and 20 per cent oxygen is only one-third as heavy as air. This has led to the use of helium-oxygen mixtures in conditions when respiration is embarrassed by obstruction. Whenever obstruction exists in the respiratory tract, an increased pressure and therefore an increased respiratory effort is needed to transport air to and from the lungs. If a helium-oxygen rather than a nitrogen-oxygen mixture is breathed, this pressure can be reduced by one-half.

Other physical properties of helium are its low coefficient of solubility and high rate of diffusion as compared with nitrogen. When helium is breathed under pressure, very little is dissolved in body fluids. In comparison, nitrogen under pressure is much more soluble in body fluids and in addition has a definite affinity for lipids. Consequently, the dangers of breathing compressed air are greatly reduced if nitrogen is replaced by helium.

Divers' Bends. When divers or other individuals working under high pressure breathe compressed air, the nitrogen of the air becomes dissolved in the body fluids. Upon return to normal pressure, this nitrogen is released from solution. Due to the high solubility and relatively slow rate of diffusion of nitrogen, a long period of time is necessary to rid the body of the excess gas. If a person breathing compressed air is brought too rapidly to atmospheric pressure, the sudden escape of nitrogen from the body fluids will result in gas emboli which produce many clinical phenomena including excruciating pains. The syndrome may prove fatal. This condition, known as "divers' bends" or "caisson disease," can only be avoided by slow decompression in order that the dissolved nitrogen may gradually diffuse from the body fluids without forming gas emboli. The necessity of slow and careful decompression is one factor which makes diving to great depths impractical.

The period of decompression can be greatly reduced if mixtures of helium and oxygen rather than air are breathed in the pressure chambers. The low solubility of helium and its poor affinity for lipids limit the amount dissolved in body fluids. The high rate of diffusion of this gas allows it to escape more readily and this factor also contributes to the shortening of the decompression period. End (1937) showed that if helium-oxygen mixtures are breathed under a pressure of three atmospheres, the subsequent decompression period need be only $\frac{1}{23}$ as long as when nitrogen-oxygen mixtures are respired. Practical use is being made of these findings.

Respiratory Obstruction. The chief use of helium in medicine is in the treatment of respiratory obstruction. Kernan and Barach (1937) outlined the sequence of events which follows obstruction in the respiratory tract. In order to force sufficient air into the lung, it is necessary to effect an increase in the intrapleural negative pressure. Under such conditions, blood enters the right chambers of the heart and the lungs more freely; but it is retarded in its departure from the pulmonary circulation as a result of the backward suction-pressure on the left ventricle as it discharges its contents into the extrathoracic aorta. Thus, marked pulmonary congestion results. To make matters worse, the increased negative pressure in the thorax exerts a suction-effect on the capillary walls and the alveoli of the lungs fill with fluid. This results in still more labored breathing; the negative pressure further increases and a vicious circle is thus established. If helium (80 per cent) and oxygen (20 per cent) are administered, rapid improvement is noted. The force required for drawing this mixture into the lungs is only one-half that necessary for air. The negative intrathoracic pressure is reduced, more oxygen reaches the alveoli, circulation is improved, and all symptoms of discomfort are relieved.

Method of Administration and Preparation. Helium may be given either in an oxygen tent (fitted with a special helium proof fabric) or, if it is desired only for a short time, it can be administered with any type of a closed circuit rebreathing apparatus. When administered in a closed circuit, it is only necessary to replace oxygen because the helium is rebreathed. Helium is an expensive gas, but with increased demands for it in medicine it should become cheaper and more readily available. It is marketed in compressed form in the usual type of steel cylinder. It is not an official drug.

Therapeutic Uses. Helium is indicated in all cases of obstruction of the respiratory tract of an acute and self-limiting nature. A few specific instances may be cited. Helium is of great value in *status asthmaticus.* In this condition the patient is often refractory to drug therapy and is in great need of oxygen inasmuch as only a limited amount of air can reach the alveoli of the lungs through the constricted bronchioles. The administration of mixtures of helium and oxygen leads immediately to partial relief, and complete relief occurs in from two to eight hours. After the patient is made more comfortable and less anoxic by the administration of helium and oxygen, the sensitivity to epinephrine often returns and this drug may again be used if necessary (Barach, 1936). Helium is valuable in the relief of symptoms arising from *inflammatory obstructions* in the air passages due to infection or to mechanical irritation resulting from instrumentation or the application of medicaments. The gas is serviceable in *anesthesia.* For example, it is useful in anesthetizing patients with tracheas compressed by adjacent growths. It is of aid to the anesthetist in an emergency when an unexpected obstruction to the respiratory tract occurs, and is helpful during partial respiratory paralysis (Eversole, 1938). These are only a few of the indications for helium. If the general principles of its action are appreciated, indications for its use will be easily recognized (Barach, 1937).

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CHAPTER 39

NOXIOUS GASES AND VAPORS

I. CARBON MONOXIDE, HYDROCYANIC ACID AND MISCELLANEOUS AGENTS

CARBON MONOXIDE

Carbon monoxide (CO) is a gas resulting from the incomplete combustion of organic matter. It is of no therapeutic value but its pharmacological properties should be thoroughly understood because of the large number of accidental and suicidal deaths which occur yearly from its inhalation.

There are many common sources of carbon monoxide. It is always present in the exhaust from automobiles where on occasion it may reach a concentration of 30 per cent. Illuminating gas also contains appreciable amounts. Although there is none present in natural gas, the so-called coal gas contains 10 per cent and water gas from 30 to 40 per cent of carbon monoxide. The illuminating gas supply of most large cities consists of water gas. In addition, other common sources of carbon monoxide are heating stoves and furnaces with insufficient draft, burning buildings, coal mine fires, etc.

Reaction with Hemoglobin. Carbon monoxide owes its toxic properties to the fact that it combines with hemoglobin to form carboxyhemoglobin (HbCO). Hemoglobin, in this form, is unavailable for the carriage of oxygen. Hemoglobin combines with the same amount of carbon monoxide as it does with oxygen and both gases react with the same group in the hemoglobin molecule. Carboxyhemoglobin, like oxyhemoglobin (HbO_2), is a dissociable compound and, in the presence of an inert gas such as nitrogen, carbon monoxide will dissociate from its combination with hemoglobin and escape from the blood. The dissociation of carboxyhemoglobin is greatest in the presence of pure oxygen, which will displace carbon monoxide in the hemoglobin molecule and convert carboxyhemoglobin to oxyhemoglobin.

If the affinity of oxygen and carbon monoxide for hemoglobin were the same, carbon monoxide would be a relatively innocuous gas. If such were the case, the amounts of oxyhemoglobin and carboxyhemoglobin formed by the breathing of air contaminated with carbon monoxide would be directly proportional to the partial pressure of these two gases in the inspired air. In other words, the concentrations of carbon monoxide and oxygen in the inhaled air would have to be equal in order to convert 50 per cent of the hemoglobin to carboxyhemoglobin. Actually, however, the affinity of carbon monoxide for the hemoglobin of man is 210 times that of oxygen. Therefore, if the concentration of carbon monoxide in the inspired air is $\frac{1}{210}$ that of oxygen, the blood will contain equal amounts of carboxy- and oxyhemoglobin. Inasmuch as the normal oxygen content of air is 20.9 volumes per cent, the above condition would exist at a carbon monoxide concentration in the air of $\frac{20.9}{210}$ or 0.1 volume per cent.

Mechanism of Toxicity. With the exception of its ability to combine with hemoglobin, carbon monoxide is a relatively inert gas. The toxic reactions which follow its inhalation are solely the result of tissue anoxia caused by the inability of the blood to carry sufficient oxygen. This point was proved very simply by Haldane in 1895. If mice are subjected to oxygen under a pressure of two atmospheres, there is sufficient oxygen in physical solution in the blood adequately to supply the metabolic requirements of the tissues. Under these conditions, the hemoglobin can all be present in the form of carboxyhemoglobin without the animals showing any symptoms of poisoning. Thus, under the ordinary circumstances of poisoning, carbon monoxide is not in itself toxic to cells. Warburg (1926) showed, however, that under exposure to very high carbon monoxide tensions there may be a combination of the gas with the cellular enzymes of respiration. This is mainly an academic point and the important fact to remember in clinical poisoning is that the tissue cells are still capable of functioning in a normal manner. The only problem is to supply them with adequate amounts of oxygen.

The reduction in the oxygen-carrying capacity of blood is proportional to the amount of carboxyhemoglobin present. However, the amount of oxygen available to the tissues is still further reduced by an additional factor. This can be understood best by comparing an anemic individual having a hemoglobin value of 50 per cent with a second person having a hemoglobin of 100 per cent, but with half of it in the form of carboxyhemoglobin. In each instance the oxygen-carrying capacity is the same. The anemic individual may show few if any symptoms whereas the person suffering from carbon monoxide poisoning will be near collapse. The explanation lies in the fact that, in the presence of carboxyhemoglobin, the dissociation curve of oxyhemoglobin is altered in such a direction that less oxygen is available for the tissues. In other words, the presence of carboxyhemoglobin interferes with the dissociation of the oxygen carried by unaltered oxyhemoglobin. For example, from the standpoint of oxygen available to the tissues, an individual with half-saturation of carboxyhemoglobin is comparable to an anemic person with only one-quarter of the normal amount of hemoglobin. Thus the mechanism of action of carbon monoxide in the production of tissue anoxia is a dual one although in both instances the primary effect is on the hemoglobin and its ability to carry and transfer oxygen to the tissues.

Factors Governing Toxicity. Two important factors govern the toxicity of carbon monoxide. These are the concentration of the gas in the inspired air and the duration of the exposure. Henderson and Haggard (1927) formulated a simple rule for the calculation of the toxic potentialities of a given amount of carbon monoxide in air. This rule states that when the product of the hours of exposure times the parts of carbon monoxide per 10,000 parts of air is a number under six, there is no perceptible clinical effect. When it reaches nine, symptoms begin and at 15 there is danger to life. For example, if air contains 0.1 per cent (10 parts per 10,000) of carbon monoxide, a sojourn in such an environment for 90 minutes would be dangerous $(10 \times 1.5 = 15)$. Such information may at times be of medicolegal importance.

The figures cited are applicable to a normal person at rest. Anemic persons are more susceptible to the gas. Increased metabolic rate enhances the severity of symptoms in carbon monoxide poisoning. It is for this reason that children will succumb earlier than adults when exposed to a given concentration of the gas. The same principle applies to the use of small animals with high metabolic rates for the detection of toxic quantities of carbon monoxide, such as the use of canaries in mines. The test animal dies before toxic symptoms are noted in man.

Symptoms of Carbon Monoxide Poisoning. The symptoms of carbon monoxide poisoning are those characteristic of anoxia. They have been closely correlated with the carboxyhemoglobin content of the blood. The following relation between symptomatology and the blood content of carboxyhemoglobin is that given by Sayers and Davenport (1930):

	Per cent of blood saturation
No symptoms	0–10
Tightness across forehead; possibly slight headache, dilatation of cutaneous blood vessels	10–20
Headache; throbbing in temples	20–30
Severe headache, weakness, dizziness, dimness of vision, nausea and vomiting, collapse	30–40
Same as previous item with more possibility of collapse and syncope; increased respiration and pulse	40–50
Syncope, increased respiration and pulse; coma with intermittent convulsions; Cheyne-Stoke's respiration	50–60
Coma with intermittent convulsions, depressed heart action and respiration, possible death	60–70
Weak pulse and slowed respiration; respiratory failure and death	70–80

The table does not imply that all these symptoms are experienced by an individual poisoned with carbon monoxide. When exposure occurs to high concentrations and the blood rapidly becomes saturated, transient weakness and dizziness may be the only premonitory warning symptoms before unconsciousness supervenes. Even these may be lacking.

Pathology of Acute Carbon Monoxide Poisoning. Carbon monoxide does not in itself cause specific pathological lesions. Rather the changes which result in the tissues following exposure to carbon monoxide are those brought about by anoxia. Consequently the tissues most seriously affected are those which are most sensitive to oxygen deprivation, such as the brain. The capillaries are the first structures to be injured by anoxia. In brain tissue this results in edema, and increased intracranial pressure is believed to be the cause of the severe headache following exposure to carbon monoxide. If exposure is prolonged and marked anoxia develops, definite cellular changes may occur. Indeed, recovery from carbon monoxide poisoning is sometimes associated with permanent damage to the central nervous system. The higher centers are much more sensitive to oxygen deprivation than the lower ones.

The heart is also sensitive to anoxia and it is thought by some that this organ may be permanently damaged from intermittent exposure to low oxygen tensions resulting from the presence of carboxyhemoglobin in the blood. For example, Beck and Suter (1938) reported a high incidence of myocardial symptoms in a large group of patients who had been intermittently exposed to carbon monoxide. Coronary thrombosis frequently developed. Symptoms were not confined to the heart but also involved the brain and other organs. They likewise point out the error of the belief that if the patient recovers from acute asphyxial symptoms all danger is past, for within three to seven days after acute exposure cardiovascular and cerebral symptoms may appear. The pathological lesions noted in the heart, brain and other organs were primarily vascular, consisting of small hemorrhages and perivascular infiltration with focal necrosis. Many of the lesions seen clinically were produced in animals by subjecting them to varying amounts of carbon monoxide.

Chronic Carbon Monoxide Poisoning. There is a question whether a condition such as chronic carbon monoxide poisoning exists. The answer to this question is largely a matter of definition. One usually looks upon chronic poisoning as a slowly developing syndrome due to the action of a drug which is constantly present in the body. In this sense, lead may be taken as a classical example of an agent capable of causing chronic intoxication. Carbon monoxide, in contrast, is rapidly excreted from the body. If an individual worked daily for several hours in an atmosphere containing carbon monoxide and was in a healthy environment for the remainder of the time, during the greater portion of each 24 hours his blood would be free of carboxyhemoglobin and his tissues would receive adequate oxygenation. Therefore, if carbon monoxide is capable of causing chronic intoxication, it must do so as a result of repeated acute exposures. The clinical evidence of Beck (1936, 1938) strongly suggests that intermittent exposure to carbon monoxide causes chronic illness. Whether this chronic illness is called chronic poisoning is a matter of little consequence. The important point is that a chronic illness develops not from the persistent action of a noxious agent but from the cumulative effects of repeated tissue injury due to intermittent exposure to carbon monoxide. Just as in the case of chronic sequelae from an acute severe exposure to the gas, the illness persists and may progress long after the noxious agent has disappeared from the body.

Diagnosis of Acute Poisoning. The presumptive diagnosis of acute carbon monoxide poisoning is usually facilitated by the fact that the victim is commonly found under circumstances that leave little doubt as to the cause of his condition. The appearance of the patient also assists in the diagnosis. Carboxyhemoglobin is bright red in color. Therefore one finds the unusual combination of asphyxia associated with a bright red color of the fingernails, mucous membranes and skin ("cherry red cyanosis"). A final diagnosis depends upon the demonstration of carboxyhemoglobin in the blood. Naturally one does not take the time to perform such a test in a severely poisoned individual but the demonstration of carboxyhemoglobin often has medicolegal significance. If a person succumbs in an atmosphere containing carbon monoxide, a postmortem blood sample will contain 75 to 90 per cent of carboxyhemoglobin. If the patient is removed from such an atmosphere while still breathing, the concentration of carboxyhemoglobin will rapidly decline, and if respiratory exchange continues to be adequate, the blood will be freed of this form of hemoglobin within a few hours.

Treatment of Carbon Monoxide Poisoning. The very first essential is to remove the patient to fresh air. As has already been stated, carbon monoxide is not toxic to tissues and all the aspects of poisoning can be ascribed to the inability of hemoglobin to carry oxygen. Therefore, in the treatment of carbon monoxide poisoning, the primary object is to get oxygen to the body cells in as high an amount as possible. If respiration has failed, artificial respiration must be immediately instituted. Pure oxygen may be administered. With high oxygen tensions, oxygen rapidly replaces carbon monoxide in the hemoglobin molecule. It also dissolves in the serum and in this manner additional oxygen can reach the cells. Still more beneficial is the simultaneous administration of carbon dioxide (five to 10 per cent) and oxygen. Carbon dioxide has a dual mechanism of action. Not only does it stimulate respiration and thus hasten the removal of the carbon monoxide, but it also decreases the pH of the blood. This lowers the affinity of hemoglobin for carbon monoxide, and thus by increasing the dissociation between carbon monoxide and hemoglobin the exchange of oxygen for carbon monoxide in hemoglobin is facilitated. By the combined use of oxygen and carbon dioxide all the carbon monoxide can be expelled from the body in less than 30 minutes, whereas oxygen alone can accomplish this in from 30 to 90 minutes. In fresh air, when respiratory exchange is normal, two hours are required (Figure 80).

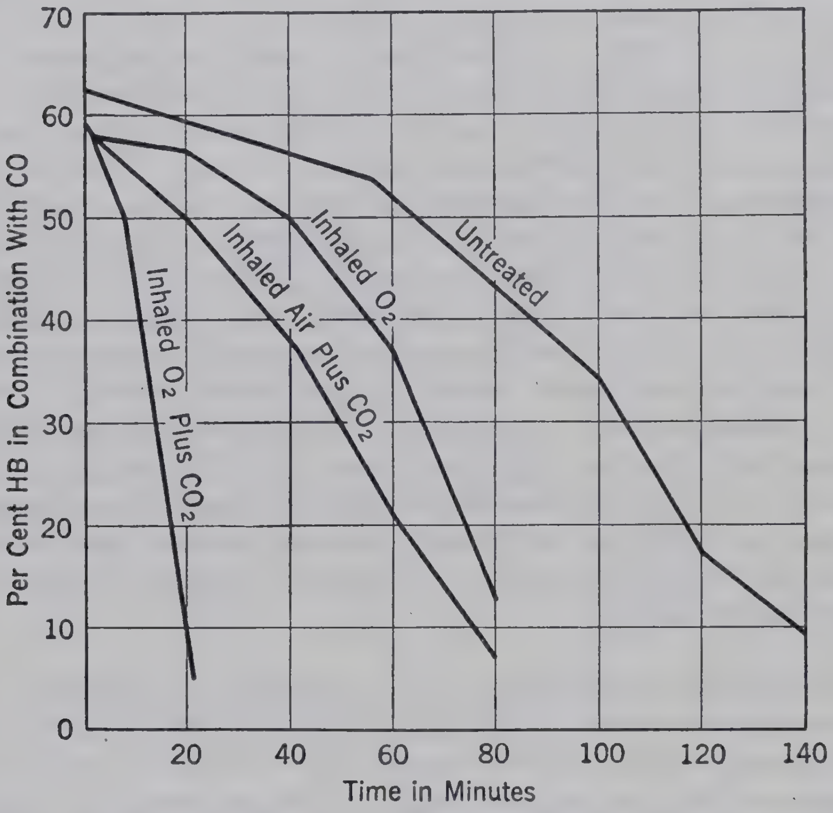

FIGURE 80. *The effect of breathing oxygen and carbon dioxide on the rate of dissociation of carboxyhemoglobin.*

Experiments were performed upon dogs asphyxiated almost to the point of death by means of illuminating gas diluted with air. Untreated animals excrete carbon monoxide slowly due to the high affinity of the gas for hemoglobin. When the oxygen tension of the blood is raised by the inhalation of pure oxygen, carbon monoxide is more rapidly displaced from its combination with the hemoglobin molecule. The addition of carbon dioxide further speeds recovery by lowering the pH of the blood, thus hastening the dissociation of carboxyhemoglobin, and by increasing the respiratory exchange. (After Henderson and Haggard, 1922. Courtesy of *The Journal of the American Medical Association.*)

Supportive treatment is also instituted. The patient should be kept warm. It also is especially important that he remain absolutely quiet in order that tissue demands for oxygen be kept at a minimum. Blood transfusion is a helpful procedure, but usually before it can be administered the patient, with proper therapy, has already eliminated most of the carbon monoxide.

The prognosis should be guarded. The possible after-effects of severe poisoning have already been described. The outcome is especially unfavorable if the patient remains in coma for an extended period. This is probably an indication that a marked degree of cerebral damage has already resulted.

At one time the injection of methylene blue was advocated in the treatment of carbon monoxide poisoning and it is still sometimes used. This compound was introduced in the belief that it could serve in the place of the tissue oxidases which were thought to be inactivated by carbon monoxide. The objections to this reasoning are: (1) there is little evidence that methylene blue can function in this capacity; (2) there is no evidence that the tissue oxidases are in the least affected by concentrations of carbon monoxide encountered in clinical poisoning; (3) even if methylene blue could function as a tissue oxidase the presence of carboxyhemoglobin precludes the possibility of sufficient oxygen reaching the tissues. Even in the face of these objections to its use, the administration of methylene blue would be no more than an innocuous though useless procedure were it not for the fact that this compound, in the dose usually given, is in itself capable of inactivating oxyhemoglobin by converting it to methemoglobin. If a patient poisoned by carbon monoxide were given methylene blue, some of the hemoglobin remaining for oxygen transport would be converted to methemoglobin and become unavailable for oxygen carriage. Experimental data showing the inefficacy and danger of methylene blue in carbon monoxide poisoning have been obtained on animals by several investigators. The sporadic clinical reports of success with methylene blue probably represent cases which have recovered in spite of irrational therapy.

HYDROCYANIC ACID

Hydrocyanic acid or prussic acid is one of the most rapidly acting of all poisons. The inhalation of the vapors of hydrocyanic acid causes severe toxic effects which lead to death within a few minutes to three hours, depending upon the concentration breathed. This rapidity of action has led to the adoption of the gas by several states for use in executing criminals. The action of hydrocyanic acid is due to the cyanide ion and thus the toxic properties of the gas are shared by all the soluble inorganic cyanide salts. The following discussion pertains to all compounds which release the cyanide ion.

The cyanides are of no therapeutic value. Prussic acid is used as a fumigating agent to rid closed quarters of insect or animal pests. Its employment should be entrusted only to those experienced in its handling.

Pharmacological Actions. The most interesting action of the cyanide ion is that which accounts for its toxic properties. The ion acts on the respiratory ferments of tissue cells to incapacitate them and thus to prevent the uptake of oxygen by tissues. In this manner it produces an asphyxial death, unique in that, whereas in all other types of asphyxia the carriage of oxygen by the blood is deficient, in this instance the blood is saturated with oxygen to its physiological limit. The tissues, however, are incapable of utilizing the oxygen. Therefore one finds that in cyanide poisoning the arteriovenous oxygen difference is less than normal. Not until the beginning of respiratory failure does the concentration of reduced hemoglobin become sufficiently high to cause cyanosis. The terms cyanide and cyanosis both come from the Greek word meaning blue, but with respect to cyanide this origin is in connection with the ability of the ion to form intense blue colors in combination with iron.

Another interesting pharmacological property of the cyanide ion is its ability to stimulate respiration. In low concentration, the ion acts on the chemosensitive receptors of the carotid body and not directly on the medulla, higher concentrations being needed for action on the medullary respiratory center. The stimulation is intense, but it is of little therapeutic value because of its short duration, and the low therapeutic index of the cyanide ion. The action of the cyanide ion to stimulate respiration has found a unique application in the *measurement of circulatory velocity.* Inasmuch as the manifestation of the action of cyanide on the carotid body is immediate, the interval between the injection of a safe dose of cyanide into a given vein and the succeeding hyperpnea is a measure of the time required for the circulation to transport the injected ions from the site of administration to the site of action.

Absorption, Fate and Excretion. The cyanide ion is readily absorbed from all tissues except the intact skin. Part of the absorbed cyanide is excreted unchanged by the lungs. The larger portion, however, is converted to the relatively non-toxic thiocyanate radical. The thiocyanate ion is distributed and excreted in a manner analogous to the halogens. The rate of conversion to thiocyanate is much too slow under ordinary circumstances appreciably to diminish the toxicity of the cyanide ion.

Cyanide Poisoning. Most deaths from cyanide are suicidal, but some arise from accidental exposure in industry. Cattle grazing on certain grasses and plants which contain cyanide in large amounts also succumb to poisoning by this agent. The symptoms of cyanide poisoning appear within a few seconds to minutes after ingesting compounds or breathing vapors containing the ion. They consist of

MEDICATION	NUMBER OF M.L.D'S OF NaCN REQUIRED TO KILL
NONE	●
NITROGLYCERIN	●
METHYLENE BLUE	●●●
SODIUM THIOSULFATE	●●●●
SODIUM TETRATHIONATE	●●●●
AMYL NITRITE	●●●●●
SODIUM NITRITE	●●●●●
METHYLENE BLUE AND SODIUM TETRATHIONATE	●●● ●●●●
AMYL NITRITE AND SODIUM THIOSULFATE	●●●●● ●●●●●●
SODIUM NITRITE AND SODIUM TETRATHIONATE	●●●●●●● ●●●●●●●
SODIUM NITRITE AND SODIUM THIOSULFATE	●●●●●●●●●● ●●●●●●●●●●●

FIGURE 81. *Comparison of action of different antidotal substances in dogs poisoned by sodium cyanide.*

Each black circle represents one minimal lethal dose (M.L.D.) of sodium cyanide. Note the relative inefficacy of methylene blue and the potentiation of antidotal action obtained by the combined use of sodium nitrite and sodium thiosulfate. (After Chen, Rose and Clowes, 1934. Courtesy of the *American Journal of the Medical Sciences.*)

giddiness, hyperpnea, headache, palpitation, cyanosis and unconsciousness. Asphyxial convulsions may precede death. Although high doses are fatal within a few minutes, cases have been reported in which death has been delayed for as long as three hours. Therefore prompt treatment can be a life-saving procedure. As long as the heart continues to beat there is an opportunity for saving the patient inasmuch as effective antidotes are available.

Treatment. Treatment for cyanide poisoning is specific and must be given rapidly if it is to prove effective. It is therefore fortunate that the diagnosis can be made by the characteristic cyanide odor on the breath (odor of "oil of bitter almonds") of the poisoned individual. This finding in association with asphyxia and cyanosis is pathognomonic. The objective in the treatment of cyanide poisoning is to produce a methemoglobinemia. Methemoglobin combines with the cyanide ion to form cyanmethemoglobin, and in this combination the cyanide is non-ionized and non-toxic. Once cyanmethemoglobin is formed, sodium thiosulfate is administered in order to convert to thiocyanate the cyanide which is subsequently released by the dissociation of cyanmethemoglobin.

The best agent to use for the formation of methemoglobin has been shown by Chen, Rose and Clowes (1934) to be sodium nitrite (Figure 81). This is given in a dose of 0.3 to 0.5 gram dissolved in 10 to 15 cc of water. Three to four minutes should be taken for the injection. If there is an appreciable delay before the solution can be prepared and injected, the patient may be tided over this period with amyl nitrite inhalations, given for thirty seconds of each two minutes. Following (but not together with) the sodium nitrite, sodium thiosulfate should be given by slow intravenous injection. The dose is 25 grams in a total volume of 50 cc administered over a ten minute period. If symptoms reappear after once being controlled, the above procedure should be repeated except that in this instance the dose is halved. If the nitrites cause a profound fall in blood pressure, epinephrine or ephedrine may be administered to control this undesired effect. Also the severity of the methemoglobinemia may be greater than desired for the purpose of cyanide detoxification, and if a severe and prolonged anoxemia results, it may be necessary to resort to the inhalation of oxygen or even to a blood transfusion. Further treatment is purely symptomatic.

Using the type of therapy cited, it has proved possible to protect experimental animals from 21 times the minimal lethal dose of cyanide (Figure 81). This treatment is seven times as effective as methylene blue, another agent which has been recommended and rather extensively employed for the treatment of clinical cyanide poisoning. Methylene blue also acts by virtue of its ability to form methemoglobin (page 870), but it is not as certain or as active in this respect as nitrite salts.

The successful treatment of cyanide poisoning in human beings with sodium nitrite and sodium thiosulfate has been reported by Ingegno and Franco (1937) and Williams (1938).

BENZOL

"Benzol" is a term used interchangeably to designate one of two substances. Chemically pure benzene, C_6H_6, is often referred to as benzol, but the name is also applied to commercial benzol, a fraction obtained from the distillation of crude naphtha, one of the products of the distillation of coal tar. Commercial benzol consists largely of benzene but it also contains such closely related chemical substances as xylene and toluene. In benzol poisoning, however, it is the benzene which is the toxic agent. Benzene should not be confused with "benzine." The latter product is obtained from the distillation of petroleum, contains a mixture of hydrocarbons, and is similar in composition to gasoline and kerosene.

Benzol is toxic when it gains access to the body by any route. Contact with the skin may result in the absorption of harmful quantities. Poisoning commonly occurs, however, as a result of the inhalation of benzol vapors. A concentration of one part of benzol vapor in 10,000 parts of air is sufficient to cause toxic symptoms. The high incidence of benzol poisoning is the result of the extensive use of the compound in industry. It is employed in the manufacture of rubber, munitions, dyes, leather, paint, etc. In addition, it is used in dry-cleaning establishments and many other commercial processes.

Benzol poisoning may be acute or chronic. Acute benzol poisoning results from the ingestion of benzol either by accident or with suicidal intent. It also follows the breathing of concentrated vapors such as may be encountered when workmen enter benzol storage tanks or large stills for the purpose of cleaning them. Chronic poisoning results from long exposure to vapors in low concentration. Benzene is excreted in the urine in the form of a conjugated sulfate and the level of organic sulfate in the urine may be used to estimate the degree of exposure (*see* Bowditch and Elkins, 1939).

Acute Poisoning. The symptoms of acute poisoning are mainly referable to the central nervous system. There is a preliminary period of excitement and restlessness. This is followed by central nervous system depression, and death results from respiratory failure. If the concentration of benzol vapor is very high, there may be an asphyxial element involved due to the breathing of an irrespirable gas. The treatment of this type of poisoning is purely symptomatic.

Chronic Poisoning. In chronic poisoning, the concentration of benzol vapor inhaled is insufficient to depress the central nervous system. The major toxic manifestations result from the action of the poison on the bone marrow. Individuals vary in their susceptibility to benzol. In general, men are more resistant to the drug than women, and the younger the person the greater the degree of sensitivity. However, there is so much individual variation that one cannot predict in any given case the response to benzol exposure. Symptoms may be delayed for months or even years after the initial contact with the chemical. Indeed, they may appear after all exposure has ceased.

Benzol may first stimulate leukocyte formation and the early indication of its action may be leukocytosis (either lymphocytic or polymorphonuclear). Death from myeloid leukemia has been reported (Erf and Rhoads, 1939). This stimulation soon gives way to a depression of the precursors of all the formed elements of the peripheral blood, namely, the red blood cells, white blood cells, and platelets. The result is an aplastic anemia. In severe cases, the erythrocyte count may be below 1,000,000 per cubic mm, with a corresponding decrease in hemoglobin. This is accompanied by all the classical symptoms and signs of anemia, namely, weakness, vertigo, palpitation, dyspnea, anginoid pain, edema, and other manifestations of tissue anoxia. Usually, however, patients with chronic benzol poisoning have a red blood cell count of approximately 50 per cent of normal.

Benzol may selectively depress the formation of leukocytes, especially granulocytes, and a severe malignant neutropenia may occur with all the clinical symptoms which characterize this condition. These include weakness, ulcerative lesions of the mouth and throat and marked toxemia. Benzol also may cause a reduction in the number of platelets, and in most cases the platelet count is lowered to less than 50,000 per cubic mm of blood. This results in bleeding from mucous membranes, ecchymoses, petechiae, sore gums and various other manifestations characteristic of symptomatic thrombopenic purpura. Coagulation time, clot retraction time and bleeding time are all increased. (*See* Hunter, 1939; Erf and Rhoads, 1939; Davis, 1940.)

The depression of any one of the myeloid hematopoietic elements may be sufficient to cause death. The poisoned individual may succumb to the aplastic anemia, granulocytopenia, thrombocytopenia or to intercurrent disease or infection. The pathological lesions associated with benzene poisoning have been described by Mallory and coworkers (1939).

Treatment. For individuals known to be exposed to benzol vapors in their working environment, prophylactic precautions should be taken. In addition to all possible methods for protection against breathing the fumes, such persons should have periodic physical examinations, including careful blood studies. In addition, the urine should be examined at intervals in order to determine the extent of excretion of benzol, which serves as an index to the degree of exposure. Once poisoning has developed, it is essential to prevent further exposure. Therapy is purely symptomatic. If anemia is very marked, blood transfusion may be advisable and the administration of iron preparations is indicated. If severe neutropenia develops, the therapeutic procedure is the same as that for any other form of agranulocytosis (page 1147). Thrombocytopenia with purpura may also require blood transfusions.

Therapeutic Uses. Benzol is no longer used in therapeutics. At one time it was employed in leukemia in order to reduce the white cell count, and in polycythemia in order to effect a reduction in the number of circulating red blood cells. The chemical has been discarded, however, because of the real danger of producing aplastic anemia and because more effective measures than benzol are available for these diseases.

HYDROGEN SULFIDE

Hydrogen sulfide is a colorless inflammable gas, easily recognized by its characteristic odor. It is highly toxic, a concentration of 0.07 per cent being sufficient to cause death. Higher concentrations are rapidly fatal. The gas is encountered in sewers and in chemists' laboratories and is used in, or is a by-product of, many industrial processes, for example, the production of sulfur dyes, carbon disulfide, the manufacture of rayon, and the refining of high sulfur-petroleum.

Symptoms. The symptoms of hydrogen sulfide poisoning vary with the concentrations inhaled. If the concentration of gas is high (1:1000), death may be almost instantaneous. With lower concentrations there occurs a rather characteristic sequence of events. The gas is a local irritant and exposure results in marked conjunctivitis with swelling of the eyelids. The mucous membranes of the respiratory passages are also affected and pharyngeal and bronchial irritation is frequent. If the gas reaches the alveolar epithelium in sufficient amount, edema of the lung may result and pneumonia is a frequent sequel. Dermatitis is also a common symptom of long exposure.

It is the systemic action of the gas, however, which is responsible for its most toxic effects. In the moist lung, hydrogen sulfide is rapidly converted to sodium sulfide as a result of its reaction with sodium salts. In the blood stream it is once again converted to hydrogen sulfide and then oxidized and converted to the nontoxic sodium sulfate. The tissues are thus deprived of the oxygen used in this oxidative process. This is the only mechanism by which the gas can cause an anoxia, although it was formerly believed that hydrogen sulfide reacted with hemoglobin to form sulfhemoglobin. It has been established, however, that the gas will combine only with methemoglobin, which is not normally present in the circulation. After death, however, methemoglobin is formed and any hydrogen sulfide present at this time will combine with it to form sulfhemoglobin.

The main symptoms of hydrogen sulfide poisoning, other than local ones, are due to the action of the gas itself upon the central nervous system. If low concentrations are inhaled, the patient suffers from headache, nausea, dyspnea, vertigo, and marked malaise. Higher concentrations first stimulate and then depress the central nervous system. Stimulation may be sufficiently marked to cause hyperpnea and convulsions, although it may be that anoxia and acidosis play contributing rôles in the development of this syndrome. Eventually respiration is depressed, and death results from respiratory failure, the heart continuing to beat for several minutes after the breathing stops.

Treatment. If respiration and tissue oxygenation can be maintained, the body will soon oxidize the toxic sulfide to sulfate. Therefore the victim of poisoning should be immediately removed to the fresh air. If he is still breathing, the administration of oxygen and carbon dioxide is helpful. If spontaneous respiration has ceased, artificial respiration combined with oxygen administration should be promptly instituted. Other measures are purely symptomatic. The sequelae to exposure are pneumonia and, if poisoning has been severe, after-effects characteristic of anoxia.

CARBON DISULFIDE

Carbon disulfide (CS_2) is widely used in industry as a solvent and in the manufacture of artificial silk. Hence, poisoning from this chemical is not uncommon. Carbon disulfide is a very volatile fluid, and although poisoning may occur from its ingestion, most cases of intoxication arise from inhalation of the vapors. Poisoning may be acute or chronic.

Symptoms. Carbon disulfide is toxic to the central nervous system. When high concentrations are inhaled, the chief symptoms are those of central nervous system depression. An initial period of excitement is followed by unconsciousness and terminal convulsions. Death results from respiratory failure. When smaller quantities of the vapor are inhaled over more extended periods of time, chronic symptoms result from extensive damage of the central nervous system. Multiple peripheral neuritis leading to paralysis is commonly observed. The optic nerve is especially vulnerable to this chemical and serious visual disturbances may result from optic atrophy. After prolonged periods of exposure, there may develop emotional instability and sexual impotence. Eventually, dementia, mania, paranoia and other psychoses may ensue. Symptoms of parkinsonism suggest that the basal ganglia may also be involved in the toxic effects of these vapors. In addition, appetite and sleep are disturbed, gastro-intestinal symptoms are common, and weakness, anemia, weight loss and general debility ensue.

Treatment. Aside from removing the patient from his environmental exposure to the gas, treatment is purely symptomatic. Recovery may take months and often the damage caused by carbon disulfide is so extensive as to preclude complete restitution of function.

GASOLINE

The vapors of gasoline in a concentration of two parts per thousand are dangerous to breathe. Higher concentrations are rapidly toxic. Workers in industry where gasoline is used as a solvent are often exposed to these vapors and symptoms may ensue. Gasoline consists mainly of the higher hydrocarbons of the methane series which depress the central nervous system in a manner similar to the anesthetic hydrocarbons. Their first action, however, is stimulation.

Symptoms. Headache, nausea, and vertigo may be the first symptoms observed. These are followed by excitement and confusion. If exposure continues, stupor or unconsciousness may supervene. In the unconscious state, muscle jactitations and eventually frank convulsive movements occur. Death results from respiratory depression.

Treatment. The patient should be removed immediately to fresh air. Respiration should be stimulated and other symptomatic therapy instituted.

ARSINE

Arsine (AsH_3, arseniuretted hydrogen, hydrogen arsenide) represents arsenic in its most toxic form. The compound is a true gas. It is not used industrially but may be accidentally formed in any process where nascent hydrogen and arsenic come in contact. For example, in the manufacture of hydrogen gas from zinc, the latter element invariably contains traces of arsenic and arsine is likely to be formed. The gas is injurious when inhaled for 30 minutes in a concentration of one part in 4000.

Arsine is toxic to red blood cells. It combines with hemoglobin and subsequently is oxidized to a toxic hemolytic compound. This reaction proceeds slowly and consequently the toxic effects of arsine are delayed. Symptoms may not appear for from six to 36 hours after exposure, depending upon the dose. They arise both from the anemia occasioned by the hemolysis and the effects on the liver and kidney of the broken red corpuscles and their released hemoglobin. The outstanding symptoms are chills, fever, nausea and vomiting, lumbar pain, a scanty urine containing free hemoglobin, red cells and casts, jaundice, and the characteristic symptoms of anemia and anoxia. In addition, the gas has a direct depressant action on the central nervous system. If recovery occurs from the acute symptoms, the patient is still likely to develop subacute arsenic poisoning.

Treatment. This includes blood transfusion if the anemia is severe, oxygen inhalation to combat anoxia, and other symptomatic measures.

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CHAPTER 40

NOXIOUS GASES AND VAPORS

II. THE WAR GASES

A number of toxic chemical agents, to which the term "war gases" has been applied, have been employed in warfare. In using this term it must be emphasized that many of the members of the group are not true gases, but rather liquids of high vapor pressure. Some are solids and depend upon an explosive force for their dispersion.

As a result mainly of propaganda, chemical warfare is viewed as one of the most brutal aspects of war. Military authorities are less severe in their criticism of chemical agents. From the standpoint of cost and effort, chemicals are extremely effective weapons. It has been estimated that gas is from four to five times more efficient than the average military agent. Regarding humaneness, it can be argued that the use of gas is one of the least brutal methods of warfare. The immediate effects of a chemical agent cause less suffering than wounds from other weapons. The ratio of fatalities to total casualties is less than one-tenth that from non-gas weapons, a feature which does not interfere with the tactical advantages of gas. Lastly the sequelae of gas poisoning cannot be compared with those caused by gunshot wounds. True, gas can produce permanent injury, but as is aptly expressed by Prentiss (1935), ". . . if the man who is gassed survives the war, he comes out body whole, as God made him, and not the legless, armless, or deformed cripple produced by the mangling and rending effects of high explosives, gunshot wounds, and bayonet thrusts."

Tactical Requirements. A chemical agent must fulfill certain tactical requirements before it can be of value in warfare.

Toxicity. It stands to reason that the toxicity of an agent to be used in chemical warfare must be high. This does not mean that the gas must be lethal, but rather that it should exert its particular action in a low concentration in order that effective amounts may be dispersed on the battlefield. The purpose of chemical warfare is as much to incapacitate as to kill opposing troops. The wounded soldier represents an obligation and an expense to his army.

Multiple Effects. A gas which has multiple effects is of more value than one which possesses only a single type of action. A chemical which produces lacrimation, vesication, and injury to the lungs is three times as great a threat as an agent which has only one of these actions.

Physical Persistency. Inasmuch as toxicity is often related to duration of action as well as to concentration, it is essential that a gas remain at the site of release in an effective concentration for a sufficient length of time to exert its toxic action. Thus most gases and vapors used in chemical warfare are heavier than air and tend to remain close to the ground. A light gas, even though it is highly toxic, is almost impossible to distribute in effective concentration by the methods employed in chemical warfare. For example, hydrogen cyanide was tested during the World War of 1914–1918, but proved useless as an offensive agent because of its high volatility. Gases and vapors vary greatly in their degree of persistency and are therefore used for different purposes. An offensive gas is one that is rapidly effective, but persists for a relatively short time. Advancing troops can then follow the gas attack without being endangered. A defensive gas is one that persists for days or even weeks, and is used to harass the enemy or cover retreats.

Duration of Effects. A gas which produces slow-healing wounds is greatly to be desired. Not only does it remove a man from action for a long period of time but it also imposes the burden of his care.

Speed of Action. The onset of action of a war gas should preferably be rapid. This reduces the chance for adequate protection to be instituted. A rapid onset of action is essential in an offensive gas, less so in one used for defensive purposes.

Insidiousness. Inasmuch as the element of surprise is essential for a successful gas attack, a gas which is invisible and odorless is of great tactical advantage.

Penetrability. The greater the penetrability of a gas through protective devices, the greater is the problem of adequate defense.

Classification. The war gases have been classified on the basis of their chemical and physical properties, persistency, degree of action and tactical advantages. For the purpose of a pharmacological discussion, however, the most valuable classification is that based upon toxicological actions. On this basis, the war gases can be divided into five major groups.

Lacrimators. The lacrimators have a more or less selective action on the eye. They cause copious secretion of tears, pain and swelling of the eye and temporary blindness. Few are toxic in the concentrations encountered, and their main use is temporarily to reduce the fighting efficiency of the enemy.

Sternutators. The sternutators are irritants which act high in the respiratory tract. They cause violent sneezing, coughing, intense headache and vomiting and thus create temporary physical disability. Many of the sternutators have a high degree of penetrability, pass the canister of the gas mask and produce effects which force the removal of the mask. This exposes the victim to other more toxic gases which are usually employed at the same time.

Lung Irritants. The lung irritants can be roughly divided into two groups depending upon their site of action. Some agents have their primary site of action on the epithelial lining of the bronchi, whereas others penetrate to the alveoli.

Vesicants. The vesicants act on the body surface to produce irritation and vesication. The skin, eyes and respiratory passages are vulnerable to their action.

Systemic Toxic Agents. These are gases which produce their toxic effects after absorption. They are rarely employed in chemical warfare, for few of them possess the tactical requirements to make them valuable offensive agents.

Lacrimators

The lacrimators may be divided into two groups, the *simple* and the *toxic*. The actions of the former group are confined to the eye, whereas the members of the latter group also affect the mucous membranes of the respiratory tract and may be classified with the lung irritants. Many of the simple lacrimators are toxic, in that they can produce death in sufficiently high concentration. However, such high concentrations are seldom encountered on the battlefield.

The lacrimators for the most part are liquids of relatively low vapor pressures. They are usually dispersed in projectiles or grenades. They act within a minute after exposure and the vapors are relatively persistent. In chemical warfare their chief use is temporarily to blind the enemy or force the use of masks and thus reduce fighting efficiency. In the World War of 1914–1918, the lacrimators were not used as extensively as the more toxic gases. In peace time they are employed for the purpose of dispersing mobs, or forcing persons from hiding.

Pharmacological Actions. The lacrimators are lipoid-soluble. Upon contact with the eye, they are not diluted by the fluids bathing the eye but rapidly penetrate into the conjunctival and corneal epithelial cells. They first produce a slight tingling sensation which soon leads to an intolerable smarting, intense lacrimation and reflex closure of the eyelids. Once the atmosphere has been cleared of the lacrimating agent, the effects wear off within a few minutes. The concentrations usually encountered seldom cause permanent injury to the eye.

Treatment. Treatment of the irritating effects of lacrimators is purely local. The eye should be copiously washed with a saturated solution of boric acid. Intense pain can be controlled by the use of local anesthetics. The unvaporized chemicals may be neutralized with strong alkali. Any chemical in the unvaporized form coming in contact with the skin may be washed off with warm sodium bicarbonate solutions. The treatment of lung injuries from lacrimators is essentially the same as for other pulmonary irritants.

Individual Agents. The lacrimators employed in the World War of 1914–1918 are presented in Table 35. The most important of these and the only member warranting discussion is chloracetophenone.

Chloracetophenone. Chloracetophenone was first prepared by American chemists too late in the course of the World War to be tried under combat conditions. Subsequent tests have shown the compound to be one of the most efficient of the lacrimators and it has been widely employed for police work. In pure form, chloracetophenone consists of colorless crystals which melt at 59 C. and boil at 247 C. The compound is stable in its molten state and this facilitates the loading of munitions. Chloracetophenone can be effectively dispersed by explosion, either in the solid form or in solution in organic solvents. A very efficient dispersion is obtained when the compound is combined with powder and the mixture burned.

Table 35

LACRIMATORY AGENTS

(Prentiss, 1937.)

SIMPLE LACRIMATORS

Agent	Structure	Minimum Lacrimatory Concentration mgm/liter	Minimum Lethal Concentration mgm/liter
Brombenzyl cyanide	$C_6H_5CHBrCN$	0.00015	0.35
Chloracetophenone	$C_6H_5COCH_2Cl$	0.0003	0.85
Ethyliodoacetate	$C_2H_5COOCH_2I$	0.0014	1.50 *
Xylyl bromide	$C_6H_4CH_3CH_2Br$	0.0018	4.50
Benzyl iodide	$C_6H_5CH_2I$	0.0020	3.00
Ethylbromacetate	$C_2H_5COOCH_2Br$	0.0030	2.30 *
Benzyl bromide	$C_6H_5CH_2Br$	0.0040	4.50
Brommethylethyl ketone	$CH_3COCHBrCH_3$	0.0126	2.00 *

TOXIC LACRIMATORS

Agent	Structure	Minimum Lacrimatory Concentration mgm/liter	Minimum Lethal Concentration mgm/liter
Bromacetone	CH_3COCH_2Br	0.0015	3.20 *
Chlorpicrin	CCl_3NO_2	0.0020	2.00 *
Phenylcarbylamine chloride	$C_6H_5CNCl_2$	0.0030	0.50 *†
Acrolein	CH_2CHCHO	0.0070	0.35 *
Iodoacetone	CH_3COCH_2I	0.0120	1.90
Chloracetone	CH_3COCH_2Cl	0.0180	2.30 †

* Indicates compounds sufficiently volatile so that lethal concentrations may be encountered at ordinary temperatures on the battlefield.

† Primarily lung irritants.

In low concentrations, chloracetophenone has a pleasant odor which has been described as resembling apple blossoms. Concentrations of the vapor as low as 0.003 mgm per liter of air produce lacrimation. If the amount in the air reaches 0.0045 mgm per liter, the environment is intolerable and a concentration of 0.85 mgm per liter is fatal after 10 minutes of exposure. High concentrations irritate the upper respiratory tract and the skin.

Sternutators

The sternutators were introduced late in the course of the World War of 1914–1918 in an attempt to overcome the defensive efficiency of the gas mask. The absorbing unit of the gas mask contains activated charcoal and soda lime. These substances effectively absorb all chemicals in the gaseous state and offer very little mechanical resistance to breathing. The sternutators are solids with high melting points and low vapor pressures. They are dispersed in the form of a finely pulverized dust by heavy explosive charges or by burning. Dust clouds persist for only a few minutes but the tiny solid particles penetrate through the adsorbents of the mask and reach the respiratory tract. The onset of action is immediate and the effects of local irritation of the upper respiratory tract are such as to force removal of the mask. The victim is then exposed to other more toxic gases which are usually employed in military warfare in conjunction with the sternutators. In order to protect from chemicals in the solid particulate state, it is necessary to incorporate a mechanical filter in gas masks. Although this effectively removes all solid particles, it greatly increases the resistance to breathing.

The sternutators may be divided into two groups, the *simple* and the *toxic*. Both groups are composed of arsenic-containing compounds. The simple sternutators are nontoxic in the concentrations usually encountered. They cause local irritation of the upper respiratory tract, but their action is a selective one on the nerve endings and the effects are not permanent because of the low concentration breathed. The irritant action of the toxic sternutators is less important than their noxious systemic effects. In addition to irritating the upper respiratory tract the compounds penetrate the bronchial tree and also produce the symptoms of arsenic poisoning. The group is more properly classified under the heading of lung irritants. The members of the sternutator group and their effective concentrations are shown in Table 36.

Pharmacological Actions. Although for tactical purposes the sternutators may be classed as simple and toxic, from a pharmacological point of view all are capable of producing toxic effects if encountered in sufficient concentration. Furthermore, they are all chemically similar, being derivatives of arsine. The sternutators may therefore be discussed as a unit.

The actions of the sternutators are those to be expected from their arsenic content. The symptoms experienced from breathing particles of arsenical compounds consist of sneezing, coughing, nausea, vomiting, pain in the chest and abdomen, headache, and irritation of the skin and eyes. If particles are swallowed, a severe enteritis soon develops. If sufficient arsenic is absorbed, there may be sensory and motor disturbances of the extremities. The chief site of action, however, is on the lungs. Epithelial destruction is evident in the trachea and bronchi, but this seldom extends to the bronchioles or alveoli. However, the circulation of the lung is generally affected and this is evidenced by marked capillary dilatation. The airways contain a thick fibrinous exudate and the alveoli become edematous. There are areas of atelectasis, emphysema and scattered hemorrhage. Secondary infection results in bronchial and lobar pneumonia.

TABLE 36

STERNUTATORS

(Prentiss, 1937.)

AGENT	STRUCTURE	MINIMAL EFFECTIVE CONC. mgm per liter
Diphenylcyanarsine........	$(C_6H_5)_2AsCN$	0.00020
Diphenylaminechlorarsine...	$(C_6H_4)_2NHAsCl$	0.00038
Diphenylchlorarsine........	$(C_6H_5)_2AsCl$	0.00043
Phenyldichlorarsine........	$C_6H_5AsCl_2$	0.00500
Ethyldichlorarsine.........	$C_2H_5AsCl_2$	0.00716
Ethyldibromarsine.........	$C_2H_5AsBr_2$	0.01080

Soldiers gassed with compounds containing arsenic apparently do not absorb sufficient arsenic to cause generalized changes in the circulatory system and parenchymatous organs. However, in laboratory studies on dogs, hemorrhagic and epithelial changes can be observed in the liver and kidneys.

Treatment. Inasmuch as there is no specific antidote for arsenic, treatment must be general and symptomatic. The pulmonary changes encountered in poisoning from the arsenical irritants are not unlike those caused by other pulmonary irritants, and therapy is discussed under the lung irritant gases. When the effects of the arsenicals remain localized in the upper respiratory passages and do not reach the lungs, therapy merely consists in removing the patient from the contaminated atmosphere and applying local therapy. A local anesthetic ointment may be employed to relieve the symptoms of conjunctival and nasal irritation. Apparently if the concentration of arsenical breathed is not sufficient to penetrate to the lungs, the local injury to the upper respiratory passages is mild in degree and recovery occurs within a few hours. Only rarely do the arsenical gases produce severe symptoms on the battlefield.

Individual Agents. *Diphenylchlorarsine.* This is a white, crystalline solid which melts at 45 C. and boils at 383 C. It has a low vapor pressure and is effective only when dispersed in the solid form. This can be most efficiently accomplished by vaporizing the solid by heat. The vapors then condense to minute particles. Dispersion by explosive force is less effective. The agent was used in the latter manner during the World War of 1914–1918 and for that reason produced few fatalities, although it was a valuable harassing agent.

Diphenylcyanarsine. This compound is a colorless, crystalline solid which melts at 31.5 C. and boils at 350 C. It is the most toxic of all agents employed in chemical warfare, the intolerable concentration being 0.00025 mgm per liter of air. It is almost impossible, however, to attain a lethal concentration by explosive dispersion. Vaporization by heat has not yet been employed in warfare.

Diphenylaminechlorarsine. This compound is the easiest and cheapest of all the arsenical agents to manufacture. It is a yellow crystalline solid with a melting point of 195 C. and a boiling point of 410 C. Its pharmacological effects appear more slowly than those of the other arsenic-containing agents, but they last for a longer period of time. Diphenylaminechlorarsine can be dispersed either by explosion or heat distillation. The compound was prepared too late in the course of the World War of 1914–1918 to receive trial but laboratory tests and police work have indicated its effectiveness.

Phenyldichlorarsine. Although this is a toxic arsenical in its own right, phenyldichlorarsine is chiefly used as a solvent for the dispersion of other arsenical agents. It is a liquid with a boiling point of 252 C. Its low vapor pressure does not permit its use in a vapor form. The compound is an active vesicant if it comes in contact with the skin.

Ethyldichlorarsine. This is the most lethal, under the conditions of use, of all the arsenical compounds. It is an oily liquid with a boiling point of 156 C. The compound is sufficiently volatile to permit the accumulation of toxic concentrations of vapor at the site of release. The vapors are non-persistent and the compound is of use as an attacking agent. Ethyldichlorarsine has three sites of action and thus fulfills the tactical requirements of multiplicity of action. It is a powerful sternutator, a toxic lung irritant and an effective vesicant. Vesication of the skin occurs after an exposure of five minutes. It is lethal if breathed in the concentration of 0.5 mgm per liter of air for 10 minutes, or 0.1 mgm per liter for 30 minutes. The compound can be dispersed by shells or from an airplane as a spray. The vesicant action is best neutralized by washing the exposed portion of the skin with a solution of sodium bicarbonate. Further therapy for the vesicant effect is described under vesicants.

Lung Irritants

The lung irritants comprise a group of agents which are gases or liquids with relatively high vapor pressures. They were the principal non-persistent casualty gases of the World War of 1914–1918. The members of this class of war gases can be placed into two main groups, the chlorine and the arsenic-containing compounds. The action of the members of the former group is confined to the lungs, whereas the arsenic-containing compounds may give rise to the systemic symptoms of arsenic poisoning. The members of the arsenical group have already been discussed under the sternutators. The lung irritants are listed in Table 37. Chlorine will be discussed as the prototype of the chlorine-containing gases following which the unique characteristics of other members of the group will be considered.

Individual Agents. *Chlorine.* The element chlorine under ordinary conditions of temperature and pressure is a greenish-yellow gas, 2.5 times more dense than air. At a temperature of 20 C., it is liquefied at a pressure of six atmospheres. One liter of liquid chlorine yields 434 liters of chlorine gas (25 C.). Chlorine may be employed in chemical warfare by releasing it from cylinders and allowing it to be carried by the wind to its destination (cloud gas attack) or by projecting it in shells. Because of its chemical reactivity, it is a simple matter to protect from chlorine by the use of gas masks. The gas can easily be detected. Therefore, from the point of view of chemical warfare, chlorine is merely of historical interest. It was the first toxic gas to be used during the World War of 1914–1918 and was extremely effective against unprepared troops. It is doubtful, however, whether chlorine will be used to any extent in future warfare. The gas is of importance, however, as an industrial poison.

Chlorine Poisoning. Chlorine gas can be detected by subjective reactions in a concentration of 1:100,000. Twice this amount causes inconvenience. One part of chlorine in 10,000 parts of air produces marked irritation of the respiratory tract and a concentration of 1:1000 is fatal after five minutes of exposure. The first effect of irritant concentrations of chlorine is to stimulate the sensory nerve endings of the respiratory tract. This causes severe pain and spasm of the larynx and bronchial musculature. There is burning in the throat, coughing, and a feeling of suffocation. Breathing is labored. If high concentrations have been inhaled, reflex irritation may cause syncope, unconsciousness and almost immediate death.

Following the first few minutes of exposure to chlorine, the bronchial muscles relax and breathing becomes easier. However, this allows the gas to gain access to the alveoli and widespread irritation of pulmonary tissue results. Capillary dilatation permits the escape of fluid from the confines of the circulatory system into the alveoli of the lungs and extensive pulmonary edema develops. The bronchi and bronchioles may also be obstructed by an inflammatory exudate.

The following serious immediate consequences result from the acute changes occurring in the lungs. (1) The presence of bronchial exudate and pulmonary edema prevents adequate oxygenation of the blood and excretion of carbon dioxide. (2) The edema and consolidation of the lungs increase circulatory resistance in the pulmonary circuit and acute right heart failure with systemic venous engorgement may result. (3) The loss of fluid from the circulation into the alveoli results in a marked anhydremia which further impedes the circulation. (4) There may be a severe acidosis due to the absorption of the Cl^- ion, accumulation of CO_2 and anoxia.

The patient in the condition described exhibits definite symptoms. Cyanosis and venous engorgement are prominent. The face, lips and tongue are blue and frequently there is visible distention of the superficial veins of the face, neck and chest. The respiration is increased in frequency and may be deeper than normal. The heart is reflexly stimulated by anoxia and the pulse is full and strong with a rate of approximately 100. Nausea and vomiting are not uncommon. A productive cough yields a yellow serous fluid which at times may be so abundant as to flow from the patient's mouth. Due to their appearance, patients in this stage of chlorine poisoning have been designated "blue cases."

Obviously, in cases of chlorine poisoning, shock may develop from peripheral circulatory collapse induced by a lack of oxygen. The patient then has an ashen color, the pulse is very fast and weak, breathing is rapid and shallow and all the symptoms of shock are present. Such patients have been designated "gray cases."

Most of the deaths caused by lung irritants result from pulmonary edema and cardiovascular failure, and usually occur from eight to 24 hours after exposure. On postmortem examination the outstanding findings in the thorax are acute inflammation of the bronchi, large edematous areas alternating with foci of emphysema and atelectasis in the lungs, and acute dilatation of the heart, notably the right ventricle.

Recovery from the acute effects of chlorine gas is initiated by the absorption of the alveolar edema fluid. The circulation is thereby rapidly improved. However, the patient still suffers from bronchitis and emphysema. He is also extremely susceptible to infection of the lungs and pneumonia is a common sequel.

The residual effects of warfare gases have been extensively studied by Gilchrist and Matz (1933). Although the pulmonary lesions resulting from exposure to chlorine gas usually completely resolve, anatomical residua are noted in approximately 10 per cent of survivors. These are principally chronic bronchitis, emphysema and pulmonary tuberculosis. Tuberculosis results from the activation by the effects of chlorine of pre-existing quiescent or arrested tuberculous foci.

Treatment. The therapeutic measures employed in the treatment of poisoning from lung irritants center around (1) assuring adequate oxygenation of the blood, (2) improving the condition of the circulation by relieving the burden on the right heart and overcoming the anhydremia and shock, and (3) relieving subjective symptoms.

The immediate administration of oxygen is indicated. The rationale for and technic of oxygen therapy have been presented. The procedures to be instituted for improving the circulation vary with the condition of the patient. There are two primary objectives: the relief of the right heart failure and venous congestion, and the restoration of fluid to the anhydremic circulation. Unfortunately, the direct administration of fluid by vein as, for example, isotonic sodium chloride solution, while relieving anhydremia, would only add to the burden of the heart. Consequently many authorities recommend bleeding as the most efficacious procedure. The withdrawal of 400 to 700 cc of blood often relieves symptoms of circulatory failure by relieving the distention of the right heart, reducing venous congestion and allowing for dilution of the anhydremic blood by the extracellular fluids. Caffeine may also be of value as a cardiac stimulant. In cases in which venous pressure is not elevated, the circulation would probably be more greatly benefited by the injection of fluid than by venesection. In the event that the patient is already in shock (gray cases), the withdrawal of blood is definitely contraindicated. In such instances shock therapy should be instituted. The acidosis attending chlorine poisoning usually corrects itself when other symptoms are relieved. However, a dangerous degree of acidosis should be combated by the administration of suitable alkalinizing solutions (page 592).

There are many procedures available for the relief of subjective distress. The inhalation of alcohol vapor or medicated steam is often helpful. Morphine may be used to mask the sensation of air-hunger, but it has the disadvantage of depressing the respiratory center. The administration of oxygen affords relief in a more physiological manner. Severe attacks of coughing may be suppressed with codeine. The discomfort of conjunctivitis which commonly results from the irritant effects of chlorine on the eye may be relieved by copious bathing of the eyes with boric acid solution and the application of local anesthetics. Photophobia should be relieved by placing the patient in a dark room. Under no circumstances should the eyes be bandaged for this prevents proper drainage of exudate.

Treatment of bronchitis, emphysema or pneumonia following chlorine poisoning is no different from the usual measures employed for these conditions.

Phosgene. Phosgene was introduced as a war gas during the World War of 1914–1918 and was responsible for more than 80 per cent of the gas casualties. It was the principal offensive gas of the Allies. The compound is a gas at temperatures above 8.2 C. The gas is colorless, 3.5 times as dense as air and has an odor resembling new-mown hay. Phosgene is comparatively inert chemically in the dry form but readily hydrolyzes in the presence of water to carbon dioxide and hydrochloric acid. In chemical warfare the gas can be dispersed in shells or used as a cloud gas in conjunction with chlorine. Due to its great sensitivity to hydrolysis, phosgene is ineffective in moist weather. The vapors are nonpersistent and the gas makes a suitable attacking agent. Efficient protection from phosgene is obtainable from the modern gas mask and the chemical has probably passed its period of usefulness in warfare.

Phosgene Poisoning. Phosgene is approximately 10 times as toxic as chlorine, exposure to a concentration of 0.5 mgm per liter of air being fatal within 10 minutes. Much lower concentrations produce lacrimation and irritation of the lungs. The symptoms and treatment of phosgene poisoning are essentially the same as those of chlorine poisoning. The chief differences observed during the course of intoxication are due to the fact that phosgene must be hydrolyzed before the irritant hydrochloric acid, which is the agent directly toxic to cells, is liberated. Consequently initial bronchial spasm and asphyxia are less severe and the greatest cellular injury occurs in the bronchioles and alveoli. In contrast, the trachea and the bronchi manifest relatively less inflammatory reaction.

An interesting feature of phosgene poisoning is the fact that there may be a latent period of an hour or two between the original irritant effects observed during the inhalation of the gas and the more drastic symptoms resulting from pulmonary edema. For this reason, an individual exposed to phosgene should be kept under observation for several hours.

Diphosgene. Diphosgene (trichlormethylchloroformate) is an oily liquid which boils at 127 C. The compound is chemically related to phosgene and upon hydrolysis breaks down to two molecules of phosgene and eventually to hydrochloric acid and carbon dioxide. Hence the pharmacological properties of phosgene and diphosgene are almost identical. However, diphosgene offers certain tactical advantages in warfare due to its physical properties. It is a liquid at ordinary temperatures, and thus can be conveniently poured into shells. The substance, however, cannot be employed for cloud-gas operations. The vapors are 6.9 times as dense as air and have a persistency of 30 minutes, three times that of phosgene. The toxic concentrations are almost identical but diphosgene produces lacrimation more readily than phosgene does. This is a disadvantage rather than an advantage in that it serves as a warning of the presence of the gas.

Chlorpicrin. Chlorpicrin, or vomiting gas, is an oily, colorless liquid which boils at 112 C. The vapors are 5.6 times as dense as air and have a sweetish odor which is described as resembling that of flypaper. Chlorpicrin is quite volatile and when incorporated with chlorine can be used for cloud-gas attacks. It can also be dispersed in projectiles. Chemically the compound is very stable, and protection from the gas depends solely upon adsorption. Chlorpicrin persists on the open ground for three hours and thus has limitations as an offensive gas.

Chlorpicrin Poisoning. The toxicity of chlorpicrin lies midway between that of chlorine and phosgene. Concentrations of two mgm per liter of air are fatal if breathed for 10 minutes, as is also 0.8 mgm per liter if breathed for 30 minutes. The gas has a multiplicity of actions. Its primary effect is to irritate the lungs and this is the basis of its lethal properties. In addition it is a strong lacrimator and also causes nausea, vomiting, colic and diarrhea. For this reason it is known as "vomiting gas." Treatment of chlorpicrin poisoning is the same as for other lung irritants.

Vesicants

The introduction of the vesicants during the latter period of the World War of 1914–1918 ushered in a new phase of chemical warfare. For the first time a gas was available against which adequate protection could not be obtained. At the time that mustard gas, the most effective vesicant, was first used, gas masks had reached such a degree of efficiency that casualties from chemicals had greatly diminished in number, and the success of attacks depended almost completely on the element of surprise. Although the vesicants were not introduced until July, 1917, this type of agent was responsible for 400,000 casualties despite the fact that the supply of the chemical was limited. The problem of combating mustard gas was unsolved at the end of the war, and the Germans, who introduced it, in turn suffered heavily when the Allies solved the problem of its manufacture in large quantities and used it in reprisal.

The individual vesicants are listed in Table 37. By far the most important of the group is mustard gas to which has been given the name "king of the battle gases."

Mustard Gas. Mustard gas is the vapor of dichlorethyl sulfide, a transparent oily liquid with a boiling point of 217 C. In high concentrations it has an odor resembling mustard, and hence its name. In order to appreciate why mustard gas has been termed "king of the battle gases," aside from the convincing evidence of the number of casualties it has caused, it is only necessary briefly to review its tactical assets and compare them with the ideal properties of a war gas. Mustard gas is highly toxic, a concentration of 0.15 mgm per liter of air being lethal within 10 minutes. Severe conjunctivitis is caused by an exposure of one hour's duration to concentrations as low as 0.001 mgm per liter. Mustard gas has multiple effectiveness. It is irritant to the eyes, causes vesication of the skin and also is a powerful lung irritant. The effects of the gas are of long duration and casualties are incapacitated for weeks. Mustard gas is extremely insidious in action and in toxic concentrations possesses little or no odor and is invisible. The vapor is extremely penetrative, neither clothes, leather or even rubber being completely impervious to it. The vapor pressure of the liquid compound is sufficiently high to permit the attainment of lethal concentrations on the battle field. The vapors are 5.5 times as dense as air and thus cling close to the ground in effective concentrations. Dichlorethylsulfide is chemically stable and can be dispersed by projectiles. It also can be sprayed from airplanes or dropped in bombs.

Table 37

LUNG IRRITANTS AND VESICANTS

(Prentiss, 1937.)

LUNG IRRITANTS

Agent	Structure	M.L.D. (10 Min. Exposure) mgm per liter
Phenyldibromarsine	$C_6H_5AsBr_2$	0.20
Phenyldichlorarsine	$C_6H_5AsCl_2$	0.26
Dibromdimethyl ether	$CH_2BrOBrCH_2$	0.40
Dichlordimethyl ether	$CH_2ClOClCH_2$	0.47
Ethyldichlorarsine	$C_2H_5AsCl_2$	0.50
Phosgene	$COCl_2$	0.50
Trichlormethylchloroformate	$ClCOOCCl_3$	0.50
Dimethylsulfate	$(CH_3)_2SO_4$	0.50
Phenylcarbylamine chloride	$C_6H_5CNCl_2$	0.50
Monochlormethylchloroformate	$ClCOOCH_2Cl$	1.00
Ethylsulfuryl chloride	$ClSO_3C_2H_5$	1.00
Methylsulfuryl chloride	$ClSO_3CH_3$	2.00
Chloropicrin	CCl_3NO_2	2.00
Perchlormethylmercaptan	$SCCl_4$	3.00
Chlorine	Cl_2	5.60
VESICANTS		
Lewisite	$CHClCHAsCl_2$	0.12
Mustard	$S(CH_2CH_2)_2Cl_2$	0.15
Ethyldichlorarsine	$C_2H_5AsCl_2$	0.50
Methyldichlorarsine	CH_3AsCl_2	0.56
Dibromethylsulfide	$S(CH_2CH_2)_2Br_2$	1.00

The outstanding disadvantages of mustard gas are its persistency and slow onset of action. Thus it is not an attacking gas. The onset of effects from mustard gas is delayed from six to 24 hours and the compound persists at the site of dispersion for weeks. Therefore it cannot be used in areas which friendly troops may occupy. Offensively, its chief use is to guard the flanks of an advancing column. Defensively, it is excellent for covering retreats. As a harassing agent it has no equal, and the morale of troops can be greatly affected by the presence of the gas. All equipment which comes in contact with mustard gas must be decontaminated, a procedure which is no small problem.

"Mustard Poisoning." The symptoms of poisoning from mustard gas are chiefly those arising from the actions of the compound on the skin, eyes and respiratory tract.

Skin. The onset of action of mustard gas on the skin is delayed, no irritant effect being noted on first exposure irrespective of the concentration. This constitutes both an advantage and a disadvantage in regard to tactical value. It reduces the efficacy of mustard gas as an attacking agent but at the same time makes the action of the compound more insidious. The delayed action of mustard gas is probably due to the fact that dichlorethyl sulfide in itself is not an irritant. Upon hydrolysis, however, hydrochloric acid is liberated. It is believed that mustard gas penetrates the skin in an unhydrolyzed form and that it is only after the compound penetrates the cell that extensive hydrolysis takes place. In keeping with this theory, hydrochloric acid is the actual vesicant agent.

From two to 10 hours after exposure to mustard gas, the skin and mucous membranes show signs of irritation. The erythema resembles a severe sunburn and is sometimes accompanied by a punctate rash. If exposure occurs to a minimal concentration of mustard gas, the reaction progresses no further and all symptoms are gone within a few days. In some cases the affected skin may turn a dark brown color, after which the pigmented epithelium desquamates. In severe cases, a bluish discoloration of the skin develops. This is accompanied by marked swelling of the epidermis and cutis, and the formation of expanding coalescing blisters filled with a clear, serous fluid which may contain sufficient protein to coagulate. The tissue under the blister is red and hemorrhagic and when exposed gives rise to severe pain and itching. It is extremely susceptible to infection. Individuals vary in the susceptibility of their skin to mustard gas, as also do different areas of the skin of a given person. The most common sites of lesions are the scrotum, anus and face. Thicker epithelium, such as that of the palms of the hands and soles of the feet, is least vulnerable. Skin burns from mustard gas heal very slowly, and if the wound is deep, scarring occurs and it is many weeks before reparative processes are complete.

Eyes. The eyes are the first site of action of mustard gas and conjunctivitis may result from exposures to concentrations so low as to produce no other effects. The severity of ocular symptoms varies, depending upon the concentration of the gas to which the victim was exposed and the duration of exposure. Thus a concentration of 1:100,000, if only experienced from three to five minutes, produces severe symptoms whereas exposure to a concentration of 1:10,000,000 must be from 12 to 24 hours in duration in order to produce comparable effects. The first ocular symptoms consist of lacrimation, a feeling of heaviness in the upper eyelids, and the impression of a foreign body in the eye. Lacrimation becomes progressively more severe and this is followed by a swelling of the eyelids and an inflammation of the conjunctivae. The extensive hyperemia results in a purulent discharge which may become so copious as to run down the side of the face. Often the eyelids become glued together. Photophobia is marked. The irritant action of mustard gas extends to the inner structures of the eye and may cause hyperemia of the ciliary body and iris. The pupil is narrow and fixed. Clouding of the cornea may also occur and the surface of the eye has a roughened appearance. The height of inflammation is reached in from three to five days. Despite the severity of the reaction, most cases recover completely if given intelligent care.

Respiratory Tract. The lesions of the respiratory tract caused by mustard gas vary in severity and extent with the nature of the exposure. In mild cases, the actions of the vapor are limited to the nose and throat and the symptoms produced are not unlike those of an acute coryza. However, the erythema of the upper respiratory tract may become progressively more severe and be accompanied by pain and the formation of crusts. The tonsils swell and the throat becomes red and granular. In severe cases the reaction extends, progressively involving the larynx and the bronchopulmonary tree. Swallowing and speaking are painful and the voice is hoarse due to inflammation of the vocal cords. In rare cases occlusion of the glottis may cause death from asphyxia. Irritation of the bronchi and bronchioles causes extensive exudation. In many cases the epithelium becomes necrotic, ulcerates and secondary infection leads to a severe bronchopneumonia.

General Effects. Other signs and symptoms of poisoning from mustard gas include headache, thirst, malaise, vertigo, giddiness, vomiting, epigastric distress and diarrhea.

Residual Effects. The most common residual effects of mustard gas are chronic bronchitis, emphysema, bronchial asthma and certain chronic disabilities of the eyes such as conjunctivitis, blepharitis, keratitis and corneal opacities. The incidence of residual reactions is higher than 25 per cent.

Treatment. The first measures are prophylactic. After the removal of contaminated clothes, the skin should be washed free of the irritant by bathing with warm water and soap and a suitable solvent. Kerosene answers this purpose. Precautions should be taken against spreading the irritant. A dusting powder of zinc oxide, boric acid, chalk and starch should then be applied. Although it is not possible to arrest the process of vesication after a certain degree of exposure has occurred, measures are available which apparently reduce the intensity of the subsequent reaction. Thus the application of cloramine-T or Dakin's solution is said to prevent the development of erythematous areas which usually form around the vesicles. Once the lesions reach the stage of vesication, treatment as for burns (page 774) should be instituted.

The eyes should be copiously and frequently washed with boric acid solution, protected from light but not bandaged, and allowed to drain freely. If the cornea is involved, the pupils should be kept dilated with atropine sulfate. The instillation of sterile liquid petrolatum offers symptomatic relief. Mild silver proteinate may be employed during the period of mucopurulent discharge. When the inflammation is subsiding, an astringent eye wash containing 0.2 per cent zinc sulfate in a solution of boric acid is beneficial.

For the lesions of the respiratory tract, only symptomatic relief can be given. The inhalation of medicated steam offers some relief. In contrast to the lung irritants discussed, mustard gas rarely causes extensive edema, and no marked disturbance in the circulation occurs. Obstruction from excessive exudation may be treated with helium and oxygen.

Chlorvinyldichlorarsine (*Lewisite*). Lewisite is a vesicant which has not yet been employed in chemical warfare, having been developed too late in the course of the World War of 1914–1918 to receive a trial. Its properties, however, are such as to indicate its value. The compound occurs as an oily amber liquid which boils at 190 C., yielding a vapor 7.1 times more dense than air. The vapor pressure of lewisite is greater than that of mustard gas and hence the compound is much less persistent. Lewisite is hydrolyzed by water to hydrochloric acid and an oxide of chlorvinylarsine (ClCH:CHAs:O). The latter compound is also vesicant, but is non-volatile.

Lewisite, better than any other war gas, fulfills the qualification of multiplicity of action. It is a vesicant, lacrimator and lung irritant and in addition possesses the systemic toxicity of arsenic-containing compounds. The onset of action of lewisite is more rapid than that of mustard gas, beginning in about one-quarter the time after exposure. The minimum irritating concentration of lewisite is 0.0008 mgm per liter of air. The vapor cannot be detected by smell until a concentration of 0.014 mgm per liter is reached. The inhalation of a concentration of 0.048 mgm per liter for 30 minutes or 0.120 mgm per liter for ten minutes is fatal. Field concentrations many times higher than the figure last mentioned can be obtained.

Systemic Toxic Agents

Attempts were made during the World War of 1914–1918 to employ gases of high systemic toxicity. The substances used, however, were found unsuitable for chemical warfare. Although most of the agents possessed a high degree of toxicity and rapidly produced death if lethal concentrations were attained, it was almost impossible to produce effective concentrations on the battlefield. Sublethal concentrations were harmless. The compounds tried included hydrocyanic acid, cyanogen bromide and cyanogen chloride.

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SECTION XI

HEAVY METALS AND METALLOIDS

The heavy metals and metalloids are conveniently discussed together provided pharmacological organization is not sacrificed in favor of the periodic table of elements. The inorganic salts of the metals and metalloids lend themselves to grouping because many of them have pharmacological and toxicological properties in common. However, in the case of the organic derivatives of the metals, a chemical classification must give way to one based upon therapeutic application. For example, it is much more pertinent to discuss the antisyphilitic drugs as a group than it is to consider together all compounds which contain arsenic. Likewise, the organic mercurial diuretics have more in common with other diuretics than with inorganic mercury salts or organic mercurial germicides. Consequently, in the following chapters the organic derivatives of the heavy metals are in most instances introduced only to show their chemical relationships to simpler inorganic salts. Also certain metals are excluded from this section because of specific pharmacological actions and therapeutic applications which determine their discussion elsewhere. For example, iron is considered in connection with other drugs acting on the blood and blood-forming organs.

There is little to be gained by a general discussion of the pharmacological properties of metals. Although metallic salts share certain properties with respect to absorption, excretion and local actions, they differ sufficiently even in these respects so that each metal must be given individual consideration.

CHAPTER 41

LEAD

The major interest in lead centers about its toxicological properties. The toxic action of lead was recognized by Hippocrates who described a severe attack of colic in a man who extracted metals. In the second century B.C., Nicander related constipation, abdominal pain, and pallor to the action of this element in the body. By the first century A.D., lead poisoning was a well-recognized clinical entity and Dioscorides fully described the syndrome. Early descriptions were of individuals obviously exposed to large amounts of lead. It was not until the seventeenth century that the more subtle forms of lead poisoning were appreciated. The first record of experimental investigations on lead occurs in a treatise on toxicology by Orfila (1814).

Lead is a slow-acting, and subtle but powerful poison. Lead poisoning has been likened to syphilis in that many of the body tissues are vulnerable to attack and the symptoms are varied. The analogy may be extended. The early symptoms are often mild and, unless detected and treated, the poisoning may progress to a severe incapacitating illness. Once the diagnosis is made, it is the duty of the physician to trace the source of the intoxication in order that others may be protected. A single source may be of potential danger to many individuals.

In its usual form, lead poisoning is a chronic disease of slow and insidious onset. If exposure to lead is slight, symptoms may take years to develop. If two individuals are exposed to the same extent, one may develop severe poisoning but the other may remain symptom-free. These facts emphasize the importance of a knowledge of the biochemical behavior of the element in the body, because the absorption, distribution and excretion of lead play major rôles in both the onset of poisoning and its treatment.

The compounds of lead are of negligible therapeutic value. *Solution of Lead Subacetate,* N.F., has been used as an astringent, but there are more effective and less dangerous astringents. *Lotion of Lead and Opium,* N.F., is an irrational mixture at one time extensively employed in the treatment of poison ivy, but now largely discarded.

Absorption. Lead is very slowly absorbed. Nevertheless, a slow constant absorption is sufficient to produce poisoning. The gradual accumulation of the element in the body is the basis for the clinical features of progressive poisoning.

Skin. It is important to consider whether the skin is a possible site of absorption of lead because many individuals, for example painters, are often smeared with lead-containing compounds. It was formerly held that considerable amounts of the metal could gain access to the body in this manner but this has been refuted by experimental studies. It is difficult to increase appreciably the urinary excretion of lead in an animal by the local application of inorganic lead salts. There are occasions, however, when the skin might prove to be an avenue of entrance. An abrasion of the cutaneous epithelium may allow the passage of the element into the systemic circulation. It is also probable that organic compounds such as tetraethyl lead can penetrate the intact skin. Of course, lead on the hands may often be transferred to the mouth, and absorption effected in this manner.

Subcutaneous and Intramuscular. The only interest in subcutaneous or intramuscular absorption is in those rare instances when lead shot or bullets are imbedded in the tissues. There are many authentic records of poisoning arising from such circumstances. Lead shot is particularly dangerous because the large surface it supplies permits significant solution and absorption of lead. Indeed, it has been reported that poisoning occurred less than a month after lead shot has been imbedded in tissue.

Gastro-intestinal Tract. This is the main site for the absorption of lead in most instances of household poisoning. The soluble salts are more readily absorbed than the insoluble. The acid gastric secretion, however, can effect solution even of metallic lead. An acid reaction in the intestinal tract favors the absorption of lead, whereas an alkaline reaction causes precipitation of the insoluble carbonate and thus reduces the amount which reaches the circulation. A diet high in calcium also reduces the extent of absorption (Lederer and Bing, 1940). After the oral ingestion of lead compounds, most of the absorption takes place in the upper duodenum.

A large portion of the ingested metal escapes absorption. This is true even after very small amounts have been swallowed. The absolute quantity reaching the circulation, therefore, is not as much related to the total amount ingested as to the duration of the sojourn of the element in the intestinal canal. For example, if 0.2 gram of lead acetate is swallowed, it is doubtful whether a sufficient amount of this dose would be absorbed to cause symptoms of poisoning. On the other hand, if the same amount is divided into 20 portions swallowed on successive days, the symptoms of plumbism would very likely be observed.

Respiratory Tract. This is an important route of absorption of lead. Most cases of industrial poisoning result from the inhalation of lead dust or fumes. It has long been recognized that the metal can gain access to the body by way of the respiratory passages but it was believed that most of the inhaled lead never reached the lungs but rather was swallowed. The ability of the respiratory membranes to absorb lead was demonstrated by Blumgart (1923) and Minot (1924), who showed that lead can be absorbed from all portions of the respiratory tract including the nasal passages. Furthermore, absorption from this channel is much more rapid and complete than from the gastro-intestinal tract.

The mechanism by which insoluble lead dusts are so efficiently absorbed by the mucous membranes of the respiratory tract can only be surmised. Lead deposited in the respiratory passages is continually subjected to chemical solution, the mechanism of which cannot be stated with certainty. Soluble lead-protein complexes may be formed. It is also possible that the high carbon dioxide tension results in an environment sufficiently acid to promote solution of lead particles. In addition, it is likely that the lead particles may be phagocytized and gain access to the circulation in this manner.

Form of Circulating Lead. There is no unanimity of opinion as to the chemical form in which lead is carried in the circulation. Most workers are of the opinion that lead is carried either as inorganic or organic phosphates, possibilities being lead diphosphate, lead diphosphoglycerate, lead and calcium phosphate, etc., any one of which is believed capable of exerting a noxious action (Aub, 1935).

Distribution and Excretion. The *distribution* of lead in the body is of fundamental importance because this is the crucial factor in the development of lead poisoning. Following absorption from the intestinal tract, the metal gains access to the portal circulation. A portion of this lead never reaches the systemic circulation for it is excreted into the bile and lost in the feces. On the other hand, lead entering the body through the lungs gains direct access to the systemic circulation (Figure 82). This may be the chief reason why poisoning occurs more readily following inhalation than oral ingestion of lead compounds. Lead in the circulation is rapidly taken up by the tissues. The highest concentrations are found in the liver and kidneys. The element does not remain long at these sites but soon migrates from the soft tissues to bone, where it is deposited in the trabeculae as the insoluble tertiary phosphate salt. The metal may remain fixed

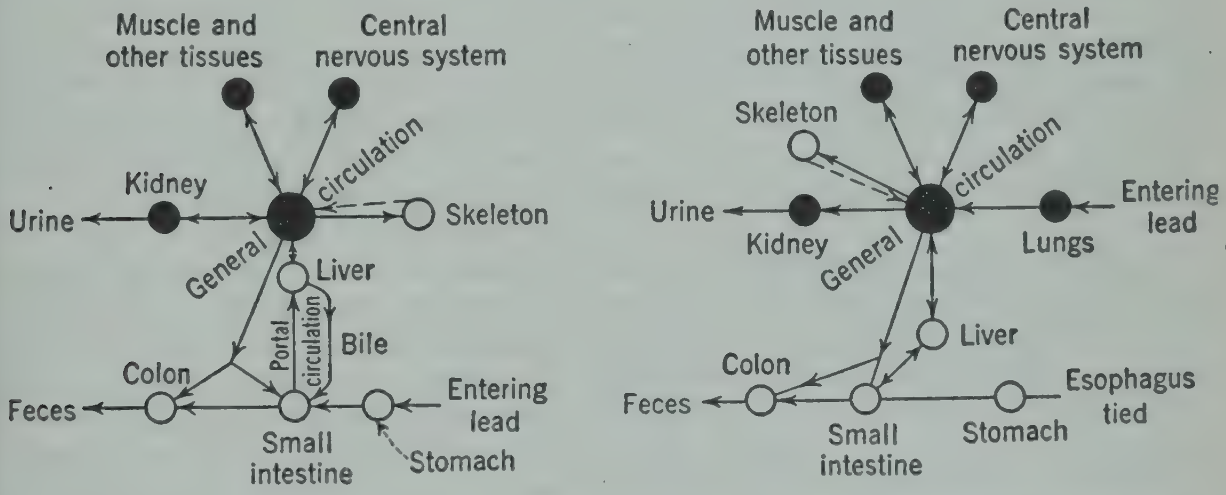
Muscle and other tissues
Central nervous system
Kidney
circulation
Urine
Skeleton
General
Liver
Portal circulation
Bile
Colon
Feces
Entering lead
Small intestine
Stomach
Muscle and other tissues
Central nervous system
Skeleton
circulation
Entering lead
Urine
Kidney
Lungs
General
Liver
Colon
Esophagus tied
Feces
Small intestine
Stomach

FIGURE 82. *The course of lead in the body after entrance from the gastro-intestinal tract (left) and from the lungs (right).*

The solid black circles represent areas susceptible to injury by lead; the hollow circles, comparatively resistant areas. (After Aub, Fairhall, Minot and Reznikoff, 1925. Courtesy of Williams and Wilkins Company.)

in the skeleton for long periods of time where it usually exerts no deleterious effects.

The main channels for the *excretion* of lead are the intestinal tract and kidneys. During exposure, much of the metal in the feces represents that which has never been absorbed. This is true even when lead is inhaled for much of it is swallowed with the mucoid secretions of the upper respiratory tract. If an individual exposed to the element is removed to a lead-free environment, the amount in the feces rapidly diminishes until it represents that portion of the absorbed lead which is being eliminated through the intestine. From a large group of patients, Aub and coworkers (1925) calculated that the average ratio of the amounts of lead excreted by the kidney to the amounts eliminated by the intestine is 1.0 to 2.5.

Kehoe and collaborators (1933) pointed out that during exposure the lead content of the feces is roughly proportional to the intensity of the exposure and serves as an approximate index to its severity. On the other hand, the amount of lead in the urine gives some indication of the quantity of metal which is free in the circulation. Urinary excretion, however, does not increase directly with the amount of lead ingested. Rather, it lags behind. This means either that absorption is proportionately less when the intake is large, or that a relatively greater amount of lead is deposited in the bones.

The balance which exists between the absorption, storage and excretion of lead is the main factor which determines the toxicity of this metal. Individuals may be described as being in lead equilibrium when excretion keeps pace with the intake and no storage of the element occurs. Should the intake be raised due to unusual exposure, however, excretion lags and storage results. If the unexcreted lead is rapidly deposited in the bones, even a relatively high intake of the metal will cause few symptoms. On the other hand, if it remains in the circulation and soft tissues, the characteristic syndrome of lead poisoning develops.

Factors Influencing the Distribution of Lead. It follows that if the distribution and deposition of lead in the body could be controlled, this would prove an important factor in the prevention and treatment of lead poisoning. Important contributions in this field were made by Aub and associates (1925). The similarity in behavior of lead and calcium with respect to the formation of their phosphate salts and their skeletal deposition gave rise to the fundamental hypothesis that the metabolism of lead and calcium is similar. They reasoned that factors favoring the deposition of calcium in bone would also favor skeletal storage of lead. Conversely, decalcification of the skeleton would liberate lead from the bones and permit its access to the circulation and its subsequent excretion. Aub was of the opinion that calcium was the one important ion in regulating the direction of the "lead stream" to and from the skeleton. He showed in both animals and patients that high calcium diets and agents favoring the deposition of calcium reduced the excretion of lead, whereas low calcium diets and procedures favoring skeletal decalcification greatly augmented the excretion of lead.

Whereas it is universally accepted that the metabolism of lead and calcium are closely linked, exception has been taken to the emphasis placed on the calcium ion to the exclusion of the rôle played by phosphates. Extending the fundamental advances in the field of calcium metabolism made by McCollum and associates, Shelling (1932, 1935) pointed out that calcification and decalcification of bone are closely related to the relative intake of both the calcium and phosphate ion. Therefore, if one desires to deposit lead in the skeleton in an insoluble form, an abundance of phosphate should be supplied. Large amounts of calcium without sufficient phosphate would exhaust the available body phosphate for the excretion of excess calcium, and thus little phosphate ion would be left for the formation of insoluble lead phosphate. Shelling also emphasized that, in order to favor the excretion of lead, diets low in calcium and high in phosphate should be employed. This diet is rachitogenic and succeeds in removing calcium and lead from bone and favors the excretion of these cations as the soluble phosphates. Experimental data obtained by Shelling in animals are supported by the clinical observations of Gray (1935) concerning the importance of phosphate in the metabolism of lead.

Other Factors Influencing the Distribution of Lead. In addition to calcium and phosphate, there are other chemical agents which influence the storage and excretion of lead. In some instances the basic mechanism of action is obviously on the calcium metabolism, but other substances have been found empirically to influence the metabolism of lead, and no satisfactory explanation of their action has been offered.

(1) *Acids and Acid-Forming Salts.* It is a well-known fact that a decrease in the pH of the blood favors solution of calcium and decalcification of bone. It is not surprising, therefore, to find that acids or potentially acid compounds increase the excretion of stored lead. Particularly effective are *hydrochloric acid, ammonium chloride,* and *phosphoric acid.* It is interesting to note that Aub and colleagues (1925) found that phosphoric acid, combined with a low calcium diet, was effective in promoting lead excretion in patients. Although at the time they attributed this effect to the acidity of the compound, it is probable that the low calcium and high phosphate intake attending this therapeutic procedure was also instrumental in promoting the mobilization of lead from bone and its subsequent excretion.

(2) *Sodium Bicarbonate.* According to Aub and coworkers (1925), the solubility of the tertiary phosphate of lead, the form in which it is present in bone, is increased by alkaline as well as by acid reactions. They therefore determined clinically the effect of sodium bicarbonate on the rate of lead excretion. Although sodium bicarbonate was not as effective as acid-producing substances, it increased appreciably the rate of lead excretion. The effect obtained was of longer duration than after the administration of acid. However, the observation that other potentially basic substances, such as sodium lactate, failed to increase the rate of lead excretion obscures the mechanism of action of sodium bicarbonate.

(3) *Iodides.* Potassium iodide has been employed since 1840 for the purpose of increasing the excretion of lead. Although its efficacy has been questioned, Aub and associates found it capable of doubling the rate of lead excretion. Potassium salts other than iodides were ineffective, whereas ammonium iodide proved to be as active as potassium iodide. From this observation, Aub concluded that the iodide ion as such promotes the excretion of lead. The mechanism of action is unknown.

(4) *Parathyroid Hormone.* In poisoned individuals, parathyroid extract promotes the excretion of lead (Aub and Hunter, 1927). The known propensity for this hormone to direct the "calcium stream" from the bones to the blood by virtue of lowering the renal threshold for phosphate is the probable basis of its mobilization of lead from the skeleton.

(5) *Vitamin D.* In the presence of an adequate intake of calcium and phosphate, vitamin D promotes the deposition of calcium phosphate and lead phosphate in the bone. Shelling (1935), however, on the basis of observations

in animals, points to the possibility that in subjects receiving vitamin D and calcium, but an inadequate amount of phosphate, the vitamin may so favor the deposition of calcium phosphate in the bone that the lead cation is deprived of the phosphate anion and stays behind in the circulation. Thus he believes that a high calcium, low phosphate diet is even less favorable to the deposition of lead in the bones in the presence of vitamin D than in its absence.

Etiology of Lead Poisoning. Lead poisoning is nearly always chronic in form because the absorption of the salts of this metal usually proceeds too slowly to allow for an acute onset of symptoms. Cases of lead poisoning can be divided into two main categories, those resulting from exposure in industry, and those occurring in the household.

Industrial Lead Poisoning. Many industrial workers are exposed to lead. Particularly dangerous industries are lead mining, smelting and refining. The manufacture of lead-containing products such as lead wire, sheet lead, plumbers' goods, bullets, storage batteries, etc., is a potential source of danger. Printers, painters and pottery glazers are also exposed to lead. In addition, many forms of lead are used in innumerable other manufacturing processes.

In the majority of cases of industrial poisoning, the route of entrance of lead is through the lungs by inhalation of dusts or fumes. Extensive research in the field of lead poisoning has led to a remarkably efficient control of this industrial poison. For example, following the recognition of the fact that lead-contaminated air is a potential source of poisoning, sanitary engineering succeeded largely in eliminating this hazard. Hygienic measures and frequent physical examinations have now reduced the incidence of serious industrial lead poisoning to a minimum. Consequently the contemporary literature on lead poisoning contains more reports of cases due to accidental household exposure than to industrial exposure.

Household Poisoning. Lead poisoning from other than industrial sources is common. In the household, the metal is often ingested by accident, and the source is usually such that repeated exposure is possible.

A few examples will illustrate this point. In a small town in New England, water was conducted through ancient lead pipes. The carbon dioxide content of the water was sufficiently high to effect appreciable solution of the lead. Upon examination, 24 per cent of 253 individuals in this town showed signs of lead poisoning. In a certain district in England, during the period 1931 to 1934, the drinking water was treated to prevent solution of the lead to which it was exposed in piping. During that time the infant mortality in the districts involved fell almost 300 per cent. Numerous instances of poisoning have been reported from the making of beer, wine and cider in vessels which contain lead due to pottery glaze. The acid reaction of the fermented beverage dissolves the lead from the glaze. Poisoning has been reported in an individual who habitually siphoned wine through a lead-containing rubber hose. A number of cases of lead poisoning in Austria in 1931 were traced to a lead counterbalance on the grinding wheel in a flour mill. Breast-fed infants have been poisoned by the mother's use of lead nipple shields (Rapoport and Kenney, 1939). Children have been poisoned by lead from chewing the paint on their cribs. In Baltimore, a number of cases of lead poisoning in poor families were traced to the burning of storage battery casings as fuel. Snuff wrapped in lead foil has been reported as a source of poisoning. An interesting case of plumbism was admitted to the New Haven Hospital in 1937. The patient was an elderly man who lived in an old country house. No other member of the family was affected, yet the source of the lead proved to be the pump supplying the drinking water. The patient was the first member of the household to arise in the morning and he habitually drank water upon arising. Sufficient lead had been dissolved during the night to reach a toxic concentration. With the removal of this stagnant water, subsequent portions were not dangerous.

The above examples give some conception of the obscure sources of lead in accidental poisoning. It is obviously the duty of the physician, when a case of lead poisoning is diagnosed, to exert every effort to discover the origin of the poison; otherwise the patient, as well as others, is likely to continue the ingestion of the metal.

Toxic Dose of Lead. The physician, especially in industry, is often desirous of learning the amount of lead which his patient is ingesting and inhaling. It is impossible to ascertain this directly, but information may be obtained from the analysis of the lead content of the blood, urine and feces. As has already been stated, the amount of lead in the feces during exposure is related to the daily intake, whereas the level in the blood and urine gives information on the extent of absorption. All individuals are exposed daily to a certain amount of lead. The metal encountered under such circumstances has been termed "normal lead." The subject of "normal lead" has been extensively investigated by Kehoe and his associates (1933, 1939), who found that the normal American adult excretes lead at the rate of 0.25 to 0.40 mgm per day. Most of this lead is present in the feces, the urinary output amounting only to 0.02 to 0.10 mgm per day, (0.02 to 0.08 mgm per liter). The normal concentration of lead in the feces is from 0.03 to 0.11 mgm per gram of fecal ash. Analysis of duplicate 24 hour samples of the food of a series of normal individuals revealed that 0.22 to 0.35 mgm of lead per day was obtained from this source. A considerable portion of the lead content of the food was found to be of natural origin, but additional quantities were derived from a variety of artificial sources. Those foods which were found most commonly above average in lead content were, in order of increasing importance, breadstuffs, meats, processed meats, ice cream, candy, leafy green vegetables, and certain fruits.

TABLE 38

URINARY LEAD CONCENTRATION IN RELATION TO LEAD EXPOSURE [†]

DEGREE OF EXPOSURE	NUMBER OF SAMPLES ANALYZED	MEAN CONCENTRATION OF URINARY LEAD FOR THE GROUP Mgm per Liter
No occupational exposure	20 (47)	0.034 (0.030) [*]
Safe occupational lead exposure	531 (96)	0.052 (0.041)
Lead exposure near toxic threshold	74	0.097
Demonstrably dangerous lead exposure	221	0.175
Very hazardous lead exposure	19	0.332

[*] Data in parentheses refer to blood analyses. Values expressed as mgm per 100 gm of whole blood.

[†] Data from Kehoe and associates, (1939) and from their unpublished data in papers presented to the Section of Industrial Hygiene of the American Public Health Association, New York, 1937, and to the American Association of Industrial Physicians, Cleveland, Ohio, 1939.

Lead can also be found in the blood of normal individuals in predictable amounts. Refined technics in the analysis for lead have established the lead content of whole blood to be approximately 0.030 mgm per 100 cc (Willoughby and Wilkins, 1938; Kaplan and McDonald, 1938; Kehoe and associates, 1939). Kehoe and associates (1933, 1939) have also shown that the blood of Mexican

Indians, living the simplest existence removed from all urban contact and subsisting on vegetable and animal products of their own cultivation, contained lead to the mean extent of 0.02 mgm per 100 grams.

The identification of lead in the blood, urine, and feces, therefore, is not indicative of lead poisoning. However, when exposure to lead has been excessive, and the symptoms of poisoning occur, normal values are greatly exceeded. Kehoe and his associates (1933, 1939) have studied groups of workmen under a variety of conditions of occupational lead exposure. Depending upon the occupation, they found that the mean daily fecal output of groups of men varied from 0.47 to 7.60 mgm, (0.09 to 0.57 mgm per gram of fecal ash). The mean lead concentration in the urine of the corresponding groups ranged from 0.05 to 0.34 mgm per liter (Table 38). Cases of lead poisoning were found among certain groups of these workmen, and from the correlation of the analytical with the clinical findings over considerable periods of time, Kehoe and his collaborators drew the following pertinent and practical conclusions. Occupational lead exposure is safe if it does not give a mean lead output of more than 0.60 mgm per day in the feces or a mean urinary concentration above 0.10 mgm per liter. Poisoning may be expected to occur under conditions in which lead occurs in the feces of workmen in excess of a mean level of 1.1 mgm per day, and in which the mean urinary lead concentration exceeds 0.15 mgm per liter. The higher the values are above these levels, the greater will be the frequency of occurrence and the severity of lead poisoning among the workmen. The threshold concentration of approximately 0.10 mgm of lead per liter in the urine, corresponds generally, under conditions of maintained lead exposure, to a blood concentration of 0.06 to 0.07 mgm. In acute lead intoxication, resulting from severe exposure, the blood concentration may rise as high as 0.30 mgm per 100 grams of whole blood, but

TABLE 39

URINARY AND FECAL CONTENT OF LEAD IN NORMAL AND EXPOSED INDIVIDUALS

(Kehoe and Associates, 1939.)

SUBJECTS	NUMBER OF SAMPLES	MEAN LEAD CONTENT OF FECES IN MGM PER SAMPLE	MEAN LEAD CONCENTRATION IN URINE IN MGM PER LITER
Mexican Indians	29	0.11	0.022
Normal American Adult	31	0.38	0.021
Normal American Adult	548	0.26	0.022
Normal American Adult	56	0.22	0.031
Medical Students	71	0.24	0.038
Garage Mechanics	81	0.51	0.047
Garage Mechanics	71	0.54	0.050
Garage Mechanics	140	0.47	0.051
Garage Mechanics	172	0.47	0.051
Unexposed Workmen	19	0.15	0.051
Workmen in Insecticide Mfg.	31	0.51	0.07
Workmen Engaged in Soldering	35	0.47	0.079
Workmen in Tetraethyl Lead Mfg.	34	0.63	0.069
Workmen in Tetraethyl Lead Mfg.	74	0.48	0.097
Storage Battery Workers	40	2.70	0.176
White Lead Workers	26	4.00	0.191
White Lead Workers	46	2.78	0.250
Brass Foundrymen	35	0.62	0.201
Storage Battery Workers	9	3.72	0.33
White Lead Workers	10	7.60	0.336

under more usual conditions of hazardous exposure, it is found between 0.08 and 0.15 mgm per 100 grams of whole blood. Many of the points mentioned are clearly illustrated in Table 39 (Kehoe and coworkers, 1939).

Despite the striking analytical results shown in this table, Kehoe does not place too much emphasis on the chemical diagnosis of lead poisoning. To quote him directly, "The diagnosis of lead intoxication must continue to rest upon skill and judgment in the elicitation and interpretation of clinical evidence. The value of dependable analytical data lies in the fact that, if they are obtained early enough, they provide a means for the appraisal of the patient's lead exposure. Thus, in view of the lack of specificity of the clinical findings in lead poisoning, we are rarely justified in concluding that such findings are due to lead without a reasonable assurance that a significant exposure to lead has occurred. On the other hand, conclusive evidence of abnormal lead absorption should not be given more than its proper weight. Lead absorption is not synonymous with lead intoxication, nor does the lead worker escape disease in other forms. Therefore, the careful observations often required in differential diagnosis may not be eliminated in favor of analytical procedure."

Chemical data are of greatest value during lead exposure or immediately after its cessation. Once the patient has been removed from exposure to lead, these data become less significant. The rate of lead output falls rapidly for a period of several weeks after which there is a prolonged and gradual diminution until the normal level is reached. The duration of the increased excretory rate varies to a large extent in accordance with the duration and severity of the lead exposure, *i.e.*, with the quantity of lead which has been absorbed into the body.

Symptoms and Signs of Lead Poisoning. The symptoms and signs of lead poisoning are so numerous and often so pathognomonic that at first glance the diagnosis of this condition appears to be a simple matter. Actually, a patient may exhibit only a few of the characteristic features. Also an early diagnosis of lead poisoning is greatly to be desired,.and it is in the incipient stage that this disease is difficult to distinguish from many poorly-defined illnesses. The more severe the intoxication, the more apparent is the diagnosis. In the late stage of poisoning, however, the damage suffered by the patient may be irreversible.

Table 40, compiled by Jones (1935), lists the important clinical and laboratory evidences of plumbism.

General Appearance. The patient's appearance and general disposition, although not diagnostic, often are suggestive of lead poisoning. Even in the very early stages of plumbism, the patient becomes moody, restive and easily excited. This condition is more readily noted by those in immediate contact with the patient than by the physician.

Pallor of the skin is one of the most constant of the early signs. The face is an ashen color and the lips are pale. The exact cause of this pallor is not known. It occurs before there is a marked change in the blood and cannot be explained on the basis of anemia. It has been suggested that lead affects capillary tone and that this is the reason for the pallor.

The *lead line,* also called the Burtonian line, is suggestive but not diagnostic of plumbism. It occurs as a black line in the gums near the border of the teeth. It merely points to the fact that lead has been absorbed. A somewhat similar pigmentation of the gums can be observed after the absorption of mercury, bismuth, silver, thallium and iron. Approximately 50 per cent of exposed individuals give evidence of the lead line but many of these will show no symptoms of poisoning. On the other hand, severe intoxication can exist with no suggestion of gingival pigmentation. The nature of the lead line is not definitely known. The majority of investigators believe that it represents lead sulfide precipitated by the reaction of hydrogen sulfide, arising from oral putrefaction, with the lead compounds circulating in the capillaries of the gums. In favor of this view is the finding that the Burtonian line seldom develops in a clean or edentulous mouth.

Table 40

COMMON SIGNS AND SYMPTOMS OBSERVED IN CASES OF PLUMBISM AND EXCESSIVE ABSORPTION OF LEAD

(Jones, 1935.)

Suggestive Evidence of Lead Absorption	Suggestive Evidence of Incipient Intoxication	Suggestive Evidence of More Advanced or Definite Plumbism
	A. GENERAL APPEARANCE	
Restive, moody, easily excited, "flustered" Lead line	Pallor Lead line Jaundice	Anemia Lead line Jaundice Emaciation "Premature aging"
	B. DIGESTIVE SYSTEM	
Persistent metallic taste Slight loss of appetite Slight constipation	Metallic taste Definite loss of appetite Coated tongue Slight abdominal colic Constipation	Metallic taste Increased loss of appetite Nausea and vomiting Coated tongue Marked abdominal colic Rigid abdomen Marked constipation Blood in the stool
	C. NERVOUS SYSTEM	
Irritable Uncooperative	Slight headache Insomnia Slight dizziness Palpitation Increased irritability Increased reflexes	Increased headache Increased insomnia Increased dizziness (ataxia) Confusion Marked reflex changes Tremor Fibrillary twitching Neuritis Visual disturbances Encephalitis (hallucinations, convulsions, coma) Paralysis
	D. MISCELLANEOUS CHANGES	
None	Muscle soreness Easily fatigued Hypotension	General weakness Joint pains Hypertension
	E. URINE EXAMINATION	
Positive test for lead	Positive test for lead Trace of albumin Few granular casts	Positive test for lead Increase in albumin and casts Hematoporphyrin present Hematuria
	F. BLOOD CHANGES	
Polycythemia Polychromatophilia Increased platelets Percentage of reticulocytes about doubled	Normal red blood cell count and normal hemoglobin Further increase in reticulocytes From 50 to 100 stippled cells per 100,000 erythrocytes	Decrease in hemoglobin and number of erythrocytes Increase in all forms of basophilic cells Increase in percentage of mononuclears Anisocytosis and poikilocytosis Nucleated red cells Decreased platelets

The line may persist for as long as seven months after the patient has been removed from lead exposure.

Jaundice observed late in poisoning is probably the result of increased destruction of red blood cells because there is no pathological change in the liver to account for it. The incidence of jaundice is not high because destruction of red blood cells proceeds slowly.

The appearance of "premature aging" is often associated with advanced lead poisoning. The patients have a stooped posture, poor muscle tone and are often emaciated. The general demeanor may remain abnormal long after exposure has been terminated.

Gastro-intestinal. Loss of appetite and slight *constipation* occur early in the course of plumbism. The patients often complain of a *persistent metallic taste.* This is a common symptom of poisoning by several heavy metals and probably is associated with the excretion of small amounts of metal in the saliva. As intoxication advances, the loss of appetite and constipation become more marked. The *tongue appears coated* and the patient may experience abdominal *colic.* In late plumbism, constipation is usually severe and the feces may be tinged with blood. *Nausea and vomiting* are not infrequent. One of the most distressing symptoms is "lead colic." This pain is paroxysmal and excruciating. During an attack, the abdominal muscles become rigid, the patient usually is doubled over, and his fists are pressed hard into his abdomen, for pressure gives some relief. In some instances, however, the abdomen is tender. Lead colic is invariably preceded by constipation and there is evidence that if constipation can be avoided, colic will not ensue. Both probably result from the action of lead on the smooth muscle of the intestinal tract. It is generally agreed that during the colic the intestinal musculature is in spasm, but how lead produces this spasm is not known. Some consider the spasm to be initiated by nerve stimulation. It is more probable, however, that lead acts directly on the musculature, although it is thought by others that the colic may be the result of anoxia due to vascular spasm. Other symptoms usually attend lead colic. The blood pressure is often elevated and the pulse is slow and hard. The skin is pale and the body temperature may fall.

The symptoms of colic may be partially relieved by heat and intestinal antispasmodics. Atropine is effective in some cases but direct muscular depressants, such as nitrites and papaverine, are more useful. Intravenous calcium chloride or gluconate sometimes affords relief. Morphine may be required to control the pain.

Nervous System. The damage to the nervous system in lead poisoning may be so severe as to be irreversible. The early symptoms are rather indefinite and consist of irritability, dizziness, headache and insomnia. However, they are of significance when they occur in conjunction with known exposure to lead. In the later stages of poisoning, lesions of the central and peripheral nervous system may develop. Two of the more common neurological syndromes are known as "lead palsy" and "lead encephalopathy."

Lead palsy is a condition characterized by severe peripheral neuritis and paralysis. The fact that the muscles paralyzed are those which are most often used, and the observation that lead causes muscle paralysis *in vitro* have fostered the belief that the action of lead may be a direct one on muscle. The typical pathology in the nerve fibers supplying these muscles, however, is a strong argument in favor of the neurogenic origin of lead palsy. Characteristically, there is atrophic degenerative neuritis with subsequent fibrosis. The lesion in the nerve is periaxial and not in the axis cylinder, and therefore the condition is curable. Should paralysis persist over long periods, however, the attending disuse atrophy of the muscles may never be completely overcome.

The nerves supplying the following groups of muscles are usually affected in plumbism: (1) the extensors of the wrist and fingers (radial nerve), (2) the extensors of the toes and foot (peroneal nerve), (3) the small muscles of the hand, and (4) the deltoid, biceps, brachialis anticus and long supinator. The first two groups are those most often affected and "wrist drop" and "foot drop," respectively, result. Rarely, the laryngeal muscles are involved.

Why lead palsy should be so discrete in its distribution is unknown. Usually only one of the muscle groups mentioned is affected. If lead palsy develops in a painter, it is almost certain to take the form of wrist drop; laborers and children commonly suffer from foot drop; tailors, from paralysis of the small muscles of the hand; smelters and kilnsmen, from scapulohumeral palsy. A generalized form of paralysis may develop in exceptionally severe lead poisoning, and results from degeneration of the anterior horn cells of the spinal cord. Cranial nerve palsies and optic neuritis may also occur.

However, the possibility that lead may have a direct action on muscle has been reopened by Steiman (1939). Working with lead-poisoned frogs, Steiman showed that the phosphocreatine content of muscle was lower than normal. Also after muscular stimulation (two-minute tetanus) there was practically no resynthesis of phosphocreatine and inorganic phosphate was lost by diffusion. Steiman suggests that such a metabolic disturbance could explain the general muscular weakness, ready fatiguability and palsy characteristic of lead poisoning.

Lead encephalopathy in adults is not often seen in the United States. However, in children it may be the presenting syndrome of lead poisoning and is more frequent than generally realized. The possibility of lead encephalopathy exists whenever the signs of increased cranial pressure appear in a young child without definite localizing signs, especially when accompanied by convulsive phenomena or evidence of meningeal irritation. This diagnosis can be corroborated by a roentgenographic examination of the metaphyses of the long bones for the characteristic lines of density. Surgical decompression of the brain may be indicated (*see* Haverfield and coworkers, 1940).

Lead encephalopathy has been variously ascribed to cerebral anemia, hemorrhage or arteriosclerosis, to uremia, or to degeneration of cortical cells. Evidence, however, favors the theory that the symptoms result from a diffuse meningitis. Patients coming to autopsy exhibit predominantly a proliferative meningitis with little or no involvement of the brain cells. The encephalopathic attack is characterized by acute mental changes, evidences of increased intracranial pressure, such as headache, insomnia, restlessness, irritability and visual disturbances, delirium, convulsions and coma. Recovery is slow and the patient may never return to normal. Mental deterioration and motor paralysis are frequent sequelae.

The neurological syndrome caused by lead may often be bizarre and lack the classical features usually associated with poisoning. For example, the disease may simulate multiple sclerosis. The interesting personal case report of Williams (1939) emphasizes this fact.

Blood Pressure. Systemic blood pressure apparently is not seriously affected in lead poisoning. Advanced lead poisoning may be associated with hypertension, but the incidence is not sufficiently high to give credence to the belief that lead is the causative factor. During episodes of lead colic, the blood pressure is usually elevated but this is probably a reflex response to pain. It is also probable that the mesenteric vessels are constricted at this time. In fact, anoxia due to vascular spasm has been considered a possible cause for the onset of lead colic.

Muscle and Joint Pain. Patients with lead poisoning frequently complain of indefinite pains in muscles. The cause is unknown. Pains in the joints are also commonly experienced. There is some evidence that exposure to lead may in some way cause an unusual deposition of urates and precipitate an attack of gout.

Urine Changes. The lead content of the urine may assist greatly in the diagnosis of plumbism. The significance of urinary lead has already been fully discussed. Unfortunately the analytical procedure is a complicated one for which the average hospital laboratory is unequipped. Hematoporphyrinuria, although a fairly common finding in advanced cases, is of questionable diagnostic value for its occurrence is neither consistent nor confined to cases of plumbism. Albumin, red blood cells and casts are also frequently found and are indicative of the toxic action of lead on the kidney.

Blood Changes. The changes in the blood picture accompanying lead poisoning are quite characteristic and often help to confirm the diagnosis. The metal affects the bone marrow and also the circulating red blood corpuscles. Jones (1935) has observed a transient polycythemia early in the course of lead exposure. He attributes this to a stimulating action of the metal on the bone marrow. More typical, however, is a secondary anemia which characterizes the later stages. The destruction of red blood cells is not sufficiently rapid to cause a profound anemia. The average finding is an erythrocyte count of 4,000,000 per cubic mm with a hemoglobin value of 70 per cent. In unusual cases, however, anemia may be severe. It probably results from the action of lead on the cell membranes, causing them to lose their elasticity and to become brittle. The cells are then ruptured by trauma during circulation and removed by the reticuloendothelial system. This hemolytic destruction is a stimulus for increased bone marrow function which is manifested by an increase in reticulocytes. This reticulocytosis is of diagnostic importance in early lead poisoning.

Basophilic stippling of red blood cells is another feature which, although not unique for lead poisoning, aids considerably in diagnosis. The origin of stippled cells is not known with certainty but it is now believed that these cells are reticulocytes so affected by lead that their reticulum has degenerated to give the cells their stippled appearance. Whitby and Britton (1933) showed that a marked reticulocytosis can be obtained by the intravenous injection of lead. Stippled cells appear later and their number remains constant until another injection of lead causes a second shower of reticulocytes. Only after this occurs does the number of stippled cells again increase.

Although the significance of stippled erythrocytes in a given case of plumbism may be variously interpreted, the following pertinent facts may be stated: (1) Stippled cells do not appear in all cases of lead poisoning. (2) Their presence in the circulation is not a definite indication of lead poisoning for they can be identified in other conditions and even in normal blood. (3) Although their number is often unrelated to the severity of the poisoning, nevertheless values for stippled cells of over five per cent are more common in lead poisoning than in any other disease.

Treatment of Lead Poisoning. The specific treatment of lead poisoning centers mainly around terminating the exposure and altering the distribution of lead in the body. If the patient is seen during an acute toxic episode, symptomatic therapy may offer temporary relief.

Morphine may be needed for the pain of lead colic but antispasmodics such as heat, atropine, nitrites, and papaverine and intravenous calcium salts should be tried. Saline cathartics are effective in relieving constipation and hastening the excretion of lead in the bowel. Encephalopathic symptoms may require sedatives, or medical or surgical measures designed to decrease the intracranial pressure. If peripheral neuritides have developed, physical measures to prevent deformities and atrophy should be instituted. Anemia should be treated with adequate amounts of iron salts.

The main objective, however, is to drive the lead from the circulation and deposit it in the bones where it is inactive. As has already been pointed out, this is most effectively accomplished by a diet high in calcium and phosphates. Milk is an ideal agent for this purpose inasmuch as its ratio of calcium to phosphorus favors calcium deposition in the bone; or calcium phosphate as such may be prescribed. An adequate intake of vitamin D should also be provided. Usually toxic symptoms can be relieved within a few days by this procedure. The same therapy should also be used in patients with chronic lead poisoning who are in poor physical condition but not suffering from an acute episode. It is desirous to transfer lead from the soft tissues and circulation to the skeleton to enable the patient to return to normal strength and good nutritive condition.

Lead in the bones will not, under ordinary circumstances, cause toxic effects. However, because acidosis will mobilize the insoluble tertiary lead phosphate from the bones, there is no guaranty that lead will remain in the skeleton. Experience has shown that infections or metabolic disorders which cause acidosis may liberate lead into the circulation. The patient thus may face the predicament of an acute toxic episode from lead superimposed on the illness which gave rise to the mobilization of the metal. If the precipitating factor is a serious condition such as pneumonia, the added burden of acute symptoms from lead may be a decisive factor in the outcome of the disease. Therefore a major therapeutic problem arises as to whether, after lead has been deposited in the bones and the patient has regained his strength, one should deliberately bring about its mobilization and subsequent excretion.

Opposing views have been taken on this problem. One group questions the wisdom of deliberately exposing a well individual to the toxic action of lead, and risking the possibility of poisoning (Gray and Greenfield, 1938). The other is of the opinion that sooner or later acute undesired mobilization may occur and that it is better deliberately to promote the excretion of skeletal lead under careful supervision, at a time when the patient is in good health and prepared to withstand the ordeal. Kehoe and coworkers (1933), however, have evidence to indicate that deleading will occur spontaneously. They analyzed the tissues of eight individuals coming to autopsy within two years after known severe lead exposure and in whom no deleading procedure was employed. In every case, the lead content of the body was within normal limits. They concluded that even after severe exposure lead will slowly leave the body and the concentration will be reduced to normal limits within six to eighteen months. On the basis of these results, it appears that little time can be gained by deliberately deleading patients. It would be of great interest to ascertain the dietary history of Kehoe's cases for the average American diet is notoriously low in calcium.

In the event that a deleading procedure is instituted, the routine employed by Gray (1935) may be adopted. The patient should be in the best possible physical condition and hospitalized during the course of treatment. The following criteria serve as a guide for safe deleading (Belknap, 1935): hemoglobin of over 80 per cent; R.B.C. count of over 4,000,000; stippled cell count of less than 5,000 per 1,000,000 R.B.C., and a urinary excretion of lead of less than 0.15 mgm per day. Mobilization of lead is accomplished by the administration of a low calcium, high phosphate diet (ratio of 1:4) combined with an acid-producing salt. Ammonium chloride or ammonium nitrate may be used in a dose of one gram every hour for eight to 10 hours daily. The use of phosphoric acid can accomplish the dual purpose of causing acidosis and providing phosphate. The dose is five cc hourly for 12 hours daily. No didactic statement can be made as to the duration of treatment. Ideally, the urine should be analyzed frequently and therapy continued until lead is no longer excreted in abnormal amounts. A single course of deleading should not be allowed to run too long for symptoms of chronic lead poisoning may develop. If large amounts of lead continue to be excreted after three weeks of treatment, therapy is stopped and reinstituted at a later date. If these precautions are taken, the process of deleading is not usually accompanied by untoward reactions.

Parathyroid extract is sometimes used to promote liberation of lead from the bones and thus favor its excretion. The dose is from 40 to 80 units daily. If this extract is employed, the patient should be hospitalized and the blood levels of calcium and phosphorus closely followed in order to avoid untoward effects.

Potassium iodide is sometimes used to favor lead excretion in ambulatory patients. Fifteen drops of a saturated aqueous solution are given twice daily for three to four days. This is repeated every three to four weeks until the patient fails to excrete additional lead in response to the medication.

Acute Lead Poisoning. Acute lead poisoning is quite rare and occurs following the accidental ingestion of lead salts, especially lead acetate (sugar of lead) and lead carbonate (white lead). The syndrome should not be confused with the acute toxic episodes occurring in the course of chronic lead poisoning. Local effects in the mouth result in a marked astringent action, thirst and a metallic taste. Nausea, abdominal pain and vomiting then ensue and the vomitus may be milky in appearance due to the presence of lead chloride. The abdominal pain is severe but is not characteristic of lead colic. The stools are black from lead sulfide. There may be diarrhea or constipation. If large amounts of lead are rapidly absorbed, the shock syndrome may develop. Acute nervous system symptoms include paresthesias, pain and muscle weakness. An acute hemolytic crisis sometimes occurs and results in severe anemia and hemoglobinuria. The kidney is damaged and oliguria and urinary changes are evident. Death may result in one or two days, but if the patient survives the acute effects, characteristic symptoms of chronic lead poisoning are likely to appear.

Treatment. Emergency therapy includes copious gastric lavage and magnesium sulfate as a cathartic to rush the ingested lead through the intestinal tract. Morphine may be needed for pain, but atropine and other antispasmodics should be given a trial. Shock therapy is instituted if the shock syndrome intervenes. The use of large amounts of calcium and phosphate as outlined above for chronic lead poisoning assists in the storage of lead in the bones and the prevention of late symptoms. Recovery from acute poisoning is usually slow.

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CHAPTER 42

MERCURY, ARSENIC AND ANTIMONY

MERCURY

Many compounds of mercury are of pharmacological interest, for this metal is extensively employed in medicine. Also, the mercuric ion is highly toxic and is frequently the cause of severe poisoning.

In a broad sense, mercury has but one pharmacological action. The drug is a "general protoplasmic poison" by virtue of the fact that the mercuric ion precipitates protein. The effects of mercury depend upon the tissues exposed to the ion and the concentration which the latter attains. To a certain extent these effects can be regulated by the route of administration of the mercury and the chemical form in which it is given. Therefore, although mercury acts in essentially the same manner on all tissue, the manifestations of this basic action vary greatly.

All mercury compounds are potential sources of the mercuric ion (Hg^{++}), a powerful poison. The relative toxicity of the different compounds depends upon the ease with which this ion is liberated. Thus, of all the preparations of mercury, mercuric chloride is the most toxic. At the other extreme are certain of the complex non-ionized organic mercurials which are safe to give even by intravenous administration.

Absorption, Distribution and Excretion. Mercury can be absorbed from all channels of the body. The soluble salts readily gain access to the circulation when taken by mouth. Mercury compounds, in suitable vehicles, are also extensively absorbed from the intact skin. Elemental mercury vaporizes to an extent sufficient to permit the inhalation of toxic amounts and may be a source of danger in industry and even in the research laboratory (Giese, 1940). Once mercury gains access to the circulation, it is rapidly taken up by the tissues. The form in which the mercuric ion circulates and is deposited in tissue is not known. After administration, it can be found in the following tissues in order of decreasing concentration: kidney, liver, spleen, intestinal wall, heart, skeletal muscle and lungs (Sollmann and Schreiber, 1936). In addition, there is evidence that mercury may be stored in the bones (Young and coworkers, 1930).

The excretion of mercury starts immediately after its administration. The main channels of excretion are the kidneys and the colon. Traces of the metal, however, appear in all body fluids and the saliva contains appreciable amounts. Naturally the drug attains its highest concentrations at the sites of excretion and this explains many of its toxic effects. Most of the mercury is excreted within six days after administration but traces of the metal may be detected for months after the drug has been given (Sollmann, Schreiber and Cole, 1935).

Mercury Poisoning. Mercury poisoning may be divided into the acute and chronic forms. Acute poisoning usually results from the oral ingestion of highly ionized inorganic preparations. Chronic poisoning as a rule follows industrial exposure or medicinal use.

Acute Mercury Poisoning. Acute poisoning is commonly caused by mercuric chloride, taken either with suicidal intent or by accident. For the latter reason, tablets of mercuric chloride are usually stained blue, made in the shape of a coffin and labeled poison. The mercuric ion precipitates all protein with which it comes in contact. The earliest evidence of the toxic action is the ashen-gray appearance of the mouth and pharynx which results from the precipitation of the protoplasm of the mucous membranes. This is accompanied by severe pain. The mucous membrane of the stomach is similarly affected and gastric pain and vomiting result. Vomiting often decides the ultimate course of the poisoning, for if the stomach is quickly and effectively emptied the chance for the patient's survival is much greater. It is important that the physician ascertain not only the amount of poison swallowed but also the interval before vomiting occurred and the thoroughness of the emesis. The poison which gains access to the small intestine causes precipitation of protoplasm and marked local irritation. This soon results in a severe, profuse bloody diarrhea. Shreds of intestinal mucosa can be identified in the stool. This local intestinal reaction may be sufficiently severe to cause profound shock, and death may result in a few hours from circulatory collapse.

The patient commonly recovers from the local symptoms, especially if vomiting has been extensive or chemical antidotes have been administered. The systemic actions of the poison start within a few hours and may last for days with death as the ultimate outcome. This phase of the poisoning is characterized by the action of the mercuric ion on the capillary walls and at the sites of excretion—the kidney, colon and mouth. Mercury imparts to the saliva a strong metallic taste. Within 24 to 36 hours, a stomatitis develops, characterized by foul breath, soreness of gums and excess salivation. Discoloration of the gingival margins similar to the lead line appears later, and infection, loosening of the teeth, and necrosis of the alveolar processes may then follow.

The toxic action of mercury on the kidney is usually the cause of death. Mercury reaches its highest concentration at this site, and the kidney may show evidence of disturbed function within a few minutes after the poison gains access to the circulation. If the local action of the drug has not been accompanied by profound shock and the circulation is adequate, the first response of the kidney may be a diuresis resulting from the suppression of tubular function. Soon, however, the renal damage becomes so extensive that oliguria and finally anuria result. Extrarenal factors may also contribute greatly to the anuria. The renal lesions produced by mercury are largely confined to the tubular epithelium but the glomeruli are also injured.

The events described combine to produce a distortion in the electrolyte pattern and distribution of the body fluids. The volume of extracellular fluid is markedly depleted as a result of the vomiting, diarrhea and the initial diuresis. Most prominent is the diarrhea, and this tends to cause acidosis which is accentuated by the inability to ingest food. In severe cases, widespread capillary damage results in marked capillary dilatation and shock. Protein and fluid are lost through the vessel walls and the circulatory volume is markedly diminished. The protein in the serum may also be reduced by loss through albuminuria and by starvation. The excretion of mercury into the colon results in colitis which intensifies and prolongs the diarrhea.

Treatment. If the patient is seen early in the course of the poisoning, treatment centers around the inactivation and removal of mercury from the gastro-intestinal tract. The best chemical antidote is protein and this is conveniently administered in the form of milk or raw eggs. A gastric tube is then passed and the stomach is washed with copious amounts of fluid. This lavage may also contain chemicals to inactivate the toxic mercuric ion. A substance recommended as an antidote for mercury is sodium formaldehyde sulfoxylate. This agent reduces mercuric salts to the insoluble monovalent (mercurous) form. It will be discussed in greater detail.

After gastric lavage is completed, attention should be quickly focused on combating the systemic toxicity of mercury. Morphine is of value for the relief of pain. One of the main objectives of therapy is to maintain the normal composition of the body fluids and protect the kidneys in so far as possible from the toxic action of mercury. The rationale and technic of this procedure have been outlined by Peters, Eisenman and Kydd (1933). Large amounts of fluid, as much as 10 liters daily, should be given parenterally. Isotonic sodium chloride solution is convenient and effective. The injection of such a solution accomplishes the dual purpose of maintaining the composition and volume of the extracellular fluids and producing a copious diuresis which protects the kidney against high concentrations of mercury. This therapy should continue unless extensive edema formation or circulatory embarrassment ensue. Often, however, the picture is complicated by anuria and shock. The anuria results mainly from kidney damage, but an inadequate circulation due to shock contributes to the faulty renal function. Shock therapy is then indicated. With the failure of renal function, acidosis is prone to develop. Starvation and diarrhea contribute to its severity. The administration of sodium bicarbonate or sodium lactate solutions will help to relieve acidosis. If the details of the blood chemistry are known, the amount of alkali needed may be estimated from the formula presented on page 592. Starvation acidosis should be combated by the intravenous administration of glucose solution and, if this is given in hypertonic concentrations, it may to some extent relieve the symptoms of shock.

The irritation attending the excretion of mercury in the colon may be somewhat mitigated by colonic irrigations. However, one is inviting the further loss of electrolytes by this procedure unless the solution introduced contains sodium chloride in isotonic concentration.

Mention has already been made of the antidotal action of sodium formaldehyde sulfoxylate. This compound was introduced in the therapy of mercury poisoning by Rosenthal (1933) on the basis of experimental data obtained on dogs. Rosenthal found that not only was this drug effective in the gastro-intestinal tract, in reducing bivalent mercury salts to the less soluble and less toxic monovalent salts, but also that the antidote could be administered parenterally to detoxify the mercury that gained access to the circulation. Thus, he could protect dogs against parenterally administered mercury. Confirmation of the antidotal action of sodium formaldehyde sulfoxylate on unabsorbed mercury in the gastro-intestinal tract has been unanimous, but the efficacy of the parenteral administration of this compound has been questioned by Modell, Gold, Winthrop and Foot (1937), on the basis of experimental observations. Rosenthal has reported excellent clinical results with this drug (1934; 1935). In his procedure, the stomach is first lavaged with 250 cc of a five per cent solution of the sulfoxylate. An additional 250 cc are then left in the gastro-intestinal tract at the termination of the washing. An intravenous injection of the drug is then given, 10 grams dissolved in 100 to 200 cc of fluid being slowly infused over a 20 minute period. In severe cases this dose may be repeated after four to six hours. A 1:1000 solution of the compound in isotonic sodium chloride solution may also be employed for colonic irrigation.

The value of therapy with sodium formaldehyde sulfoxylate has been questioned by Monte and Hull (1940) who reported no success with the compound in the treatment of 40 cases of mercury poisoning. They believe that it might possibly be of value if given immediately after the ingestion of mercury, but seldom are patients seen this early. Monte and Hull are inclined to the opinion that sodium formaldehyde sulfoxylate may actually be detrimental if given after the symptoms of poisoning have developed and consider its repeated use inadvisable. Until more is known about the value of sodium formaldehyde sulfoxylate, one should use it only in conjunction with the more conservative course of therapy previously described.

Prognosis in Acute Poisoning. The prognosis in cases of acute poisoning depends to a large extent upon the amount of mercury taken and the interval between ingestion of the poison and vomiting. If one gram of mercuric chloride is ingested and vomiting does not occur for 10 minutes, the prognosis is poor. Most patients die if this amount is retained for 15 minutes. If larger amounts have been ingested, immediate gastric evacuation does not always insure that recovery will ensue.

Chronic Mercury Poisoning. Chronic mercury poisoning results from exposure to small amounts of mercury over extended periods of time. It is encountered in industries which utilize mercury or its salts, and also may result from mercury medication. The symptoms characterizing this condition are stomatitis, colitis, progressive renal damage, loss of appetite, nutritional disturbances, anemia and peripheral neuritis. There is also involvement of the central nervous system as evidenced by behavior changes, mental depression, insomnia, and occasionally hallucinations.

The *treatment* of chronic poisoning is purely symptomatic. The patient should, of course, be removed from all contact with mercury. Attention is then centered on improving his nutritive state. Chronic mercury poisoning responds slowly to therapy and the patient may remain in ill health for years.

There is a form of mercurial poisoning designated as *subacute.* It usually arises from improper medication. The symptoms are the same as those of chronic poisoning except that the nervous system and general nutritive condition of the patient are not as seriously affected. Treatment consists in removal from exposure and supportive therapy.

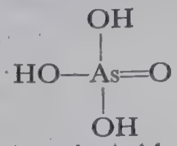
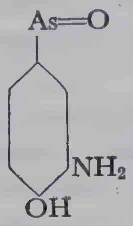
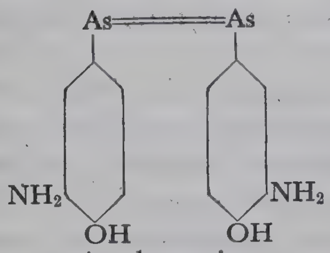
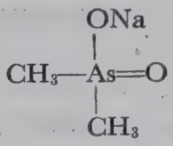
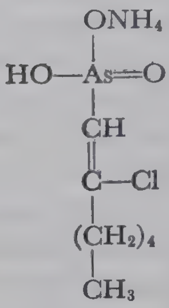
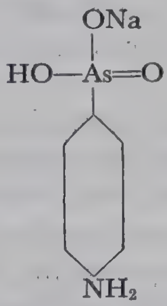
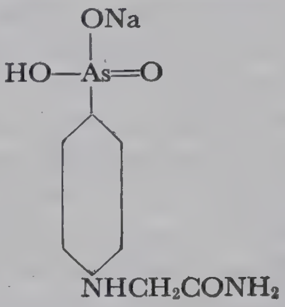
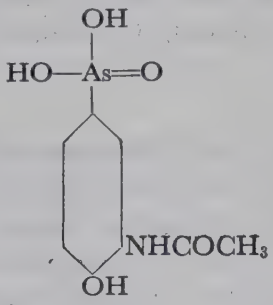
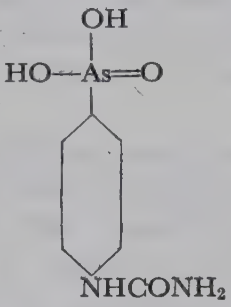
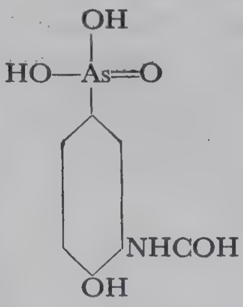
Pharmacological Actions and Therapeutic Uses. The specific actions of mercury are considered elsewhere in connection with the several therapeutic uses of the mercury compounds. The ionizable mercuric salts, by virtue of their ability to precipitate protein, are general protoplasmic poisons. As such they are employed as antiseptics (page 852). Certain organic compounds of mercury also liberate the mercuric ion readily enough to exert an antiseptic action (page 854). Also certain mercury salts when locally applied are effective parasiticides and fungicides. The antitreponemal action of mercury allows for the use of mercury compounds in the prophylaxis and treatment of syphilis (page 986). Certain complex organic mercurial compounds suppress reabsorptive activity of renal tubules and are employed as diuretics (page 639). Mercurous chloride is used as a cathartic (page 803).

ARSENIC

Arsenic was known as a therapeutic agent to the ancient Greeks and Romans, and was the favorite tool of the professional poisoners of the Middle Ages. Although organic arsenical compounds are of major importance in the treatment of syphilis and certain other protozoan diseases, other uses of arsenic in modern therapeutics are decidedly limited.

Table 41

CHEMICAL CLASSIFICATION AND STRUCTURE OF ARSENICALS

	Trivalent	Pentavalent
Inorganic	As_2O_3 Arsenic Trioxide (Arsenous acid) $KAsO_2$ Potassium Arsenite	 $\mathrm{HO{-}\overset{\displaystyle OH}{\underset{\displaystyle OH}{As}}{=}O}$ Arsenic Acid
Organic	 Mapharsen  Arsphenamine Derivatives of Arsphenamine	 $\mathrm{CH_3{-}\overset{\displaystyle ONa}{\underset{\displaystyle CH_3}{As}}{=}O}$ Sodium Cacodylate  $\mathrm{HO{-}\overset{\displaystyle ONH_4}{As}{=}O}$, $\mathrm{As{-}CH{=}C(Cl){-}(CH_2)_4{-}CH_3}$ Solarson  Atoxyl (Sodium Arsanilate)  Tryparsamide  Acetarsone  Carbarsone  Treparsol

Chemistry. Were it not for the efforts of the chemist, arsenic would be merely another toxic chemical agent. In its inorganic form, the element is a powerful poison with few therapeutic applications. In certain organic combinations, however, arsenic acquires new properties and uses.

The arsenical compounds used medicinally are best classified with respect to their chemical composition. On this basis, they are divided into the trivalent and pentavalent, and the inorganic and organic arsenicals. Table 41 depicts the chemistry and the interrelation of the therapeutically important preparations.

The various types of arsenical compounds are employed for widely different purposes. Consideration will be limited at this juncture to the inorganic arsenicals and those organic preparations which liberate inorganic arsenic in the body. The others will be discussed in connection with their major therapeutic applications, syphilis and amebiasis. However, for purposes of general orientation, a short resumé of the characteristic action of the different arsenicals is presented.

Inorganic Versus Organic Arsenic. The division of the arsenicals into inorganic and organic is the most basic one that can be made, for this sharply defines the compounds with respect to their properties and uses. Inorganic arsenicals are powerful poisons, highly toxic to all cells and generally employed for their effects on the tissues of the body. Organic arsenicals are less toxic, probably active in the organic form, and very poisonous to certain protozoa. The objective in their use is to produce a minimal effect on body tissue and a maximal one on invading organisms. They are employed in the treatment of treponemiasis, trypanosomiasis, spirillosis and other protozoan infections.

An exception to this description exists in the case of those organic arsenicals which slowly liberate inorganic arsenic in the body. There are two such compounds, sodium cacodylate and solarson. These drugs may be used interchangeably with inorganic arsenic and are not employed against protozoa.

Trivalent Versus Pentavalent Arsenic. There is considerable evidence to show that arsenic compounds are active only in the trivalent form. It is believed that the body reduces pentavalent arsenicals to the trivalent form and that this accounts for the activity of the arsenic compounds of higher valency. For medicinal purposes, inorganic arsenic is used only in the trivalent form. The pentavalent arsenic acid is presented in Table 41 only for the purpose of showing its basic relation to the pentavalent organic derivatives.

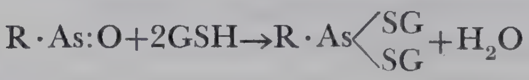
Despite the fact that all evidence points to a conversion of the pentavalent organic compounds to a trivalent form in the body, with respect to therapeutic application a sharp division can be made between the organic arsenicals on the basis of valency. The trivalent organic arsenicals are highly treponemicidal and their chief use is in the treatment of syphilis. The pentavalent organic arsenicals are active against the more highly developed protozoan forms and are valuable in the treatment of trypanosomiasis and amebiasis. Again, it may be pointed out that two pentavalent organic compounds, sodium cacodylate and solarson, are not used against parasitic infections, but liberate inorganic arsenic in the body and are employed interchangeably with the inorganic arsenicals. In all the more stable organic arsenicals, the arsenic is attached to a benzene ring, whereas in those compounds liberating inorganic arsenic, the arsenic is attached to an aliphatic chain.

INORGANIC ARSENIC

Pharmacological Actions. *General.* Arsenic is a "general protoplasmic poison," a fact which explains the variety of systemic reactions to this element. The basic mechanism by which arsenic injures cells has been the subject of research for many decades. Arsenic is not an active protein precipitant, and its cellular action can in no way be likened to that of a poison such as mercury. When arsenic reaches a cell in effective concentration, it is only slowly poisonous and there is an appreciable time interval between the moment of contact and the first evidence of toxic action. This led to the belief that arsenic acted by interfering with cellular oxidations. It was thought that arsenic behaved as an oxidizing and reducing agent in the cell by virtue of its conversion back and forth between the penta- and trivalent form (Binz, 1897). There were many facts, however, which did not fit this theory. Voegtlin, Dyer and Leonard (1923), reinvestigating the problem, were impressed with the great reactivity between arsenite and hydrogen sulfide as follows:

$$As_2O_3 + 3H_2S \rightarrow 3H_2O + As_2S_3$$

They therefore considered it likely that arsenic compounds might react with the sulfhydril (SH) groupings in cells and in this way interfere with cellular oxidations. In support of this theory, it was observed that compounds containing the SH grouping decreased the *in vitro* activity of trivalent arsenicals against trypanosomes and also delayed the symptoms of arsenical poisoning in mammals. Voegtlin and associates believed it likely that trivalent arsenicals reacted in the following manner with the sulfhydril compounds of the cell:



$$R\cdot As{:}O + 2GSH \rightarrow R\cdot As\begin{matrix}\diagup SG \\ \diagdown SG\end{matrix} + H_2O$$

In the presence of high concentrations of arsenic, this reaction would eventually impair cellular respiration sufficiently to cause cell death. Rosenthal and Voegtlin (1930) demonstrated that glutathione can protect rats against a lethal dose of sodium arsenite or an organic arsenical. (*See* page 961 for other phases of this theory of arsenical action.)

Another interesting effect of arsenic on cells is the arrest of cell division. This may also be related to the chemical affinity of the element for the SH grouping. Dustin (1933) has shown that sodium cacodylate can arrest mitosis and produce nuclear abnormalities. This action is similar to that of colchicine. Arsenates also inhibit cellular enzymes as, for example, nuclease and phosphatase (Maver and Voegtlin, 1937).

Local Action. Inorganic arsenic is a weak protein precipitant and has no chemical effect on dead tissue. Local application to live tissue at first produces only mild irritation. After prolonged contact, however, the element is very injurious to cells and causes extensive necrosis. This local effect is more pronounced on rapidly proliferating tissue, such as cancer, a finding which conforms to the hypothesis of Voegtlin already discussed. Because of this property, arsenic has been incorporated in many quack "cancer-pastes." The effects of local application are too superficial to be of value in surface carcinomas; the deeper cells are untouched by the poison; and the victim is subjected to extensive tissue ulceration.

Circulation. One of the most pronounced actions of arsenic is on the circulatory system, but this is purely of toxicological interest. Arsenic is one of the most potent of capillary poisons. After large doses, the vessels dilate to an extreme, lose their impermeability to proteins and allow the escape of plasma from the confines of the circulatory system. This injury involves all capillary beds, but it is most pronounced in the splanchnic area. The capillary dilatation results in a marked fall in blood pressure. In the early stages of arsenic poisoning, this fall may not be extensive because the arterioles are not as yet affected and they are still capable of compensatory constriction. Later, however, in addition to arteriolar damage, the loss of plasma results in a severe reduction in circulating blood volume so that the blood pressure cannot be maintained by reflex circulatory readjustment, and it then falls to a shock level. The heart muscle is also depressed by high doses of arsenic and this may contribute to the circulatory failure.

Gastro-intestinal Tract. The capillary bed of the gastro-intestinal tract is very sensitive to arsenic and dilates widely as a result. This cannot be attributed to a local effect of the arsenic in the lumen of the bowel for hyperemia at this site is marked even after parenteral administration. Small doses of arsenic cause only moderate vasodilatation. In the use of arsenic as a "tonic," presumably these slight circulatory changes in the bowel may result in increased secretion and absorption. Larger amounts of arsenic cause an extreme capillary dilatation and injury. Exudation of plasma results and the escaping fluid collects in vesicles under the gastro-intestinal mucosa. These "blisters" eventually rupture, epithelial fragments are cast off and there is a direct loss of plasma into the intestinal tract where it coagulates. The presence of this fluid and the irritant action of arsenic on the bowel lead to increased peristaltic activity and the passage of characteristic stools, known as "rice water" stools. Soon the feces become bloody. This type of dysentery in many ways resembles that associated with various diseases, especially cholera. Vomiting frequently follows the action of arsenic on the intestinal tract and the vomitus may be bloody. The gastro-intestinal symptoms of arsenic poisoning may be so gradual in onset that one may not associate them at first with the action of arsenic, especially if there is no obvious history of ingestion of the poison.

Kidney. The action of arsenic on the renal capillaries, tubules, and glomeruli may cause severe renal damage. The first effect is on the glomerulus. The vessels dilate, allow the escape of protein and swell so as to fill the glomerular capsule. Varying degrees of tubular necrosis and degeneration occur. The anhydremia resulting from the loss of fluid through other capillary beds and the low blood pressure contribute to the oliguria characterizing arsenic poisoning. The urine contains protein, red blood cells, and casts.

Skin. The action of arsenic is presumed to enhance the nutrition of the skin by virtue of vasodilatation and thus lead to a "milk and roses" complexion. It is also claimed that the hair of animals is improved and therefore arsenic is utilized by animal fanciers and breeders. Prolonged use of arsenic, however, leads to an abnormal proliferation of epithelium. Eventually this action proceeds to atrophy and degeneration. Skin eruptions are common after arsenic medication. Arsenic is deposited in the hair and nails and its detection at these sites is often of medicolegal importance.

Central Nervous System. Chronic use of or exposure to arsenic may lead to peripheral neuritis. In severe cases, there may also be involvement of the spinal cord. Upon local application, arsenic in high concentrations will inhibit respiration of medullated nerves and block impulse conduction. This action on nerves can be retarded but not prevented by SH compounds (Schmitt and Skow, 1935).

Blood. Arsenic affects the function of bone marrow and alters the cellular composition of the blood, but the mechanism of this action is obscure. The vascularity of the bone marrow is increased. In pernicious anemia, the number of immature red blood cells is elevated by arsenic but there is a decrease in the number of mature forms. In a normal individual, moderate doses of arsenic lower the red blood cell count and large amounts cause morphological changes with the appearance of megalocytes, and microcytes. Arsenic also inhibits the formation of leukocytes when this is excessive, and this action is the basis for the use of inorganic arsenicals in leukemias.

Metabolic Effects. The effect of arsenic on metabolism is obscure and ill-defined. The drug has the reputation of being an effective "tonic" but this is undeserved. The tonic action of arsenic is in all probability the early manifestation of toxic effects. For example, arsenic may increase blood flow, especially in the splanchnic area, by an early toxic action on capillaries. This presumably leads to a more effective absorption from the intestinal tract. The increased circulation to the skin may temporarily improve the nutrition of that tissue. Also, early occult edema due to capillary damage may be mistaken for a gain in weight. There is some evidence that metabolism is decreased after the administration of therapeutic doses of arsenic. The output of carbon dioxide and nitrogen is diminished. Supposedly this is the result of the effect of the drug on cellular respiration. It is claimed that such a decrease in the oxidative processes of the body favors nutrition and growth; but, from what is known of the action of arsenic, the mechanism by which this effect is obtained is none other than cellular asphyxiation. A tonic acting in this manner seems to be of questionable value. Furthermore, if the therapeutic dose of arsenic is exceeded only slightly, toxic actions may become apparent. In arsenic poisoning, nitrogen elimination is increased, because an extensive tissue degeneration occurs in many organs. The drug is particularly toxic to the liver and produces fatty infiltration and central necrosis.

Attempts to demonstrate the tonic action of arsenic in animals have consistently met with failure. Under controlled conditions, there is no dose of arsenic which, when added to the diet of experimental animals, will improve their nutritive state. Rather, the element has been found to be detrimental to normal growth and development.

Tolerance. It has been claimed that individuals become tolerant to arsenic. This belief has arisen from the fact that the mountaineers of Styria and the Tyrol eat arsenic habitually and this practice supposedly gives them great strength and endurance. That arsenic eaters can ingest large amounts of this element without noxious effects can probably be explained by the fact that they take arsenic orally in the form of a relatively insoluble coarse powder. To a large extent, the ingested arsenic escapes absorption. Animals receiving arsenic parenterally develop no tolerance.

Absorption, Distribution and Excretion. Soluble salts of arsenic are absorbed from all mucous membranes and parenteral sites of administration. Arsenic contained in ointments may be appreciably absorbed from the skin. The element rapidly leaves the blood stream and is deposited in the tissues in combination with nucleins. Arsenic is stored mainly in the liver, kidney, walls of the gastrointestinal tract, spleen, and lungs, Much smaller amounts are present in the muscles and nervous tissue. Deposition in the hair starts within two weeks after administration and arsenic stays fixed in this site for years. It is also deposited in bone and retained there for long periods.

Arsenic is slowly excreted in the urine and feces. After parenteral administration, a greater proportion is excreted by the kidneys than following oral ingestion. Excretion starts within two to eight hours but it may take 10 days for complete elimination of arsenic after a single dose, and up to 70 days after repeated administration. This slow excretion is the basis for the cumulative toxic action of arsenic.

Arsenic Poisoning. Arsenic was the popular poisoning agent of the Middle Ages and remained in favor with criminals until early in the twentieth century.

Many factors combined to give rise to this popularity. Arsenic was easy to obtain. The onset of symptoms could be produced gradually and made to simulate disease. Arsenic compounds have little taste and could easily be administered in food without detection. Embalming fluid formerly contained arsenic, and once the victim was embalmed the evidence for convicting the poisoner was obscured. Laws prohibiting the use of arsenic in such fluids, the development of chemical methods for detecting minute amounts of arsenic, and the alertness of the medical profession in the recognition of the symptoms of arsenic intoxication have greatly reduced the incidence of criminal poisoning by this agent.

Arsenic poisoning, however, continues to be prevalent. The drug is sometimes taken with suicidal intent. Arsenic may be accidentally ingested, especially by children, for it is the chief ingredient of many insecticides and rat poisons. Its use as an insecticide spray on fruits and vegetables may lead to the ingestion of toxic amounts. The Federal government has recognized this danger and placed a legal limit on the arsenic content of farm produce. Despite this legislation, it is impossible to analyze all foodstuffs coming to market and occasionally fresh fruits and vegetables, especially if consumed without thorough washing, are the source of arsenic poisoning.

Medication with arsenicals frequently gives rise to symptoms of poisoning. If the physician does not appreciate the cumulative action of arsenic compounds, the patient may continue to take his medication over a long period and the symptoms of chronic poisoning will then appear. To emphasize this point, Cannon (1936) states that if an individual suffering from psoriasis complains of vague systemic symptoms, arsenic poisoning should immediately be suspected for it is highly probable that the patient has received improper arsenic medication for his skin disorder.

Chronic arsenic poisoning also results from exposure to arsenic in industry. The element is widely used in paints, dyes, cosmetics and insecticides.

Acute Arsenic Poisoning. Acute arsenic poisoning commonly results from the oral ingestion of inorganic arsenicals. The toxic dose of arsenic is about 100 mgm when taken in the form of a trivalent inorganic salt. Arsenic is much less toxic in organic combination for the active element is only slowly released. When powdered arsenic trioxide is swallowed, the toxicity depends largely upon the physical character of the powder, that is, whether it is fine or coarse.

The time of onset of symptoms varies directly with the rate of absorption. If arsenic is ingested with a meal, symptoms may be delayed for as long as 12 hours. This may be a point of considerable medicolegal importance. Usually, however, gastro-intestinal discomfort is experienced within an hour after the poison is taken. Constriction of the throat and difficulty in swallowing may be the first symptoms to appear. Excruciating gastric pain, which is aggravated by pressure, soon follows. Persistent and projectile vomiting is characteristic. The vomitus may first consist of a "rice-water" fluid but later it becomes mucoid, bile-tinged and bloody. Diarrhea progresses from ordinary fluid evacuations to the passage of "rice-water" stools, and ultimately to bloody discharge. The urine is scanty, albuminous, bloody and eventually may be completely suppressed. The patient often complains of marked skeletal muscle cramps. A severe thirst due to fluid loss is characteristic and poisoned individuals may drink large amounts of water. The muscle cramps may be caused by the distortion in the electrolyte pattern and distribution of the body fluids resulting from the replacement with water of the isotonic fluid lost from the intestinal tract (*see* miners' cramps, page 590). As the loss of fluid from the intestinal tract and other capillary beds proceeds, symptoms of shock appear. The skin becomes cold, damp and pale, the pulse rapid and weak, the blood pressure very low and the respiration depressed. Coma and death may result. A terminal anoxia may initiate convulsions. In severe poisoning, death can occur within an hour but the usual fatal period is 24 hours.

Treatment of Acute Poisoning. Symptoms of arsenic poisoning are often delayed until considerable absorption of the poison has occurred. Despite this fact, copious gastric lavage and saline cathartics should be given if the poison was taken orally. This is particularly true if powdered arsenic was ingested because this material may remain in the stomach for some time. It was formerly thought that gastric lavage with a freshly prepared mixture of ferric hydroxide and magnesium oxide was an effective chemical antidote, but this is only true if it is administered immediately after the arsenic has been ingested. Fluid loss is prominent and all efforts should be directed as soon as possible toward maintaining the composition, distribution and volume of the extracellular fluids. Therefore, *the patient is treated for shock.* Morphine is of great value in controlling pain. Further symptomatic treatment is instituted as indicated.

Chronic Arsenic Poisoning. The symptoms of chronic arsenic poisoning usually result from the repeated administration of or continuous exposure to small amounts of arsenic. Chronic arsenic poisoning is insidious in onset. The first symptoms are those which attend many disorders. They consist of weakness, languor, loss of appetite, occasionally nausea and vomiting, and diarrhea or constipation. As poisoning progresses, symptoms become more definite and characteristic. Congested conjunctivae, catarrhal inflammation of the nose, throat and larynx, sneezing, hoarseness and coughing all simulate an acute coryza. Stomatitis and salivation are also present. Dermatitis is a frequent finding and takes many forms. Increased pigmentation known as *arsenic melanosis* may be observed especially on the neck, eyelids and nipples, and in the axillae. Keratosis of the palms and soles is another common feature of chronic poisoning. Desquamation and scaling of the skin may initiate an exfoliative dermatitis involving all the epithelial structures of the body. The liver may swell due to arsenic and obstruction of the bile ducts results in jaundice. The renal glomeruli and tubules are damaged. Edema, especially of the eyelids, face and ankles, is evidence that many capillary beds are being affected by the drug. The loss of hair and nails is another frequent occurrence in severe chronic arsenic poisoning.

As intoxication advances, the nervous system is prominently involved. Arsenical encephalopathy is the descriptive term used to designate the apathetic idiotic condition which results from long severe exposure. Peripheral neuritis not unlike that occurring in lead poisoning develops and results in a motor and sensory paralysis of the extremities. Usually the legs are more severely affected than the arms. Motor paralysis is preceded by marked sensory disturbances and pains in the joints.

The function of the bone marrow is seriously impaired by arsenic and chronic poisoning is characterized by severe blood dyscrasias. All elements of the myeloid tissue are depressed and aplastic anemia is the most common blood disorder encountered.

The most common *early signs of chronic arsenic poisoning* are *diarrhea, skin pigmentation, hyperkeratoses,* and *selective edemas,* especially of the lower eyelids and ankles. Other signs and symptoms which should arouse suspicion of arsenic poisoning include garlic odor of the breath or perspiration, excessive salivation or sweating, stomatitis, generalized itching (which may mark the onset of dermatitis or hepatitis), sore throat, coryza, lacrimation, numbness, burning or tingling of the extremities, dermatitis, vitiligo and alopecia. If arsenic poisoning is suspected and no history of exposure to arsenic can be obtained, it may be necessary to resort to chemical analysis of the excretions to establish the diagnosis.

Treatment of Chronic Poisoning. There is no satisfactory therapy for chronic arsenic poisoning and the individual symptoms must be dealt with separately. There is an extensive literature on the use of sodium thiosulfate, especially for severe arsenical dermatitis, but opinions conflict as to the value of this agent. The alleged action of sodium thiosulfate is to increase the rate of excretion of arsenic in the urine. Young (1928) and Mattice and Weisman (1937) could observe no such effect in patients although Ayres and Anderson (1938) claim that the renal excretion of arsenic is significantly increased by this agent. In an extensive experimental study Muir and associates (1940) also failed to observe any effect of thiosulfate on the excretion of arsenic. Likewise there is no agreement as to the influence of sodium thiosulfate on the clinical course of toxic reactions to arsenic. Many dermatologists and syphilologists use the drug routinely. On the other hand, Moore (1933) states that he has seen no evidence of any benefit from thiosulfate after a long and thorough trial. Primary consideration, therefore, must be given to the removal of the source of poisoning and to the relief of symptoms. Blood dyscrasia and peripheral neuritis are treated symptomatically. Repeated blood transfusions may be needed if aplastic anemia occurs. Recovery from peripheral neuritis may be incomplete even after a long period of muscle reeducation. Dermatitis usually yields to mild local measures. (*See* also the treatment of arsphenamine reactions, page 966.)

Preparations. *Inorganic Arsenic Preparations. Arsenic Trioxide,* U.S.P., B.P. (arsenous acid, arsenious acid, arsenous oxide), consists of a white powder, colorless, transparent crystals or white, opaque crystals, slowly soluble in water to the extent of one part in 65. The compound is seldom used as such, but rather is usually prescribed in the form of *Solution of Potassium Arsenite* (Fowler's Solution), U.S.P., *Arsenical Solution,* B.P. Both are colorless, odorless solutions with a slightly saline taste, containing 1.0 gram of arsenic trioxide in 100 cc of solvent (dilute potassium bicarbonate solution so that the acid is present in the form of the potassium salt).

Organic Preparations Yielding Inorganic Arsenic. Sodium Cacodylate, U.S.P. The formula for this compound may be found on page 736. It is a white powder freely soluble in water and alcohol. In the tissues, sodium cacodylate is first converted to cacodylic oxide and then to inorganic arsenic. The substance is excreted partially unchanged, in the form of the oxide, and as inorganic arsenic. After a single administration of a therapeutic dose (200 mgm), about one-third of the arsenic is excreted within 24 hours. Traces appear in the urine for about four weeks.

The cacodylates have a strong garlic-like odor and receive their name from the Greek word *kakodes* meaning foul-smelling. This property is likely to inconvenience the patient inasmuch as it imparts a garlic odor to the breath and perspiration.

The pharmacological actions and toxic effects of the cacodylates are similar to those of inorganic arsenic. Due to their slower release of arsenic, these compounds are less toxic per given amount of arsenic than inorganic preparations. However, this is only true if they are administered by hypodermic injection. After oral ingestion, inorganic arsenic is likely to be freed rapidly by the action of the acid gastric juice and serious poisoning can result from ingesting an amount that would be perfectly safe to inject. The usual dose of sodium cacodylate is 200 mgm by the hypodermic route, 60 mgm by the oral. This represents a rare instance when the hypodermic dose of a drug is larger than the oral. Sterile ampules of sodium cacodylate (0.3 gram per cc) are official in the N.F.

Solarson, N.N.R. The formula of solarson is given on page 736. This compound has properties similar to the cacodylates but the claim is made that the contained arsenic is better utilized. Solarson is marketed in ampules containing one cc of a one per cent solution. It is given by intramuscular or subcutaneous injection and the dose is one to two cc (10 to 20 mgm).

Therapeutic Uses of Inorganic Arsenic. Arsenic at one time enjoyed considerable use as a tonic. It was also extensively employed in secondary anemia, especially chlorosis, but it is doubtful whether the drug is beneficial in these conditions. Indeed, it may be potentially harmful. Two diseases which may respond favorably to medication with inorganic arsenic are *psoriasis* and *leukemia.*

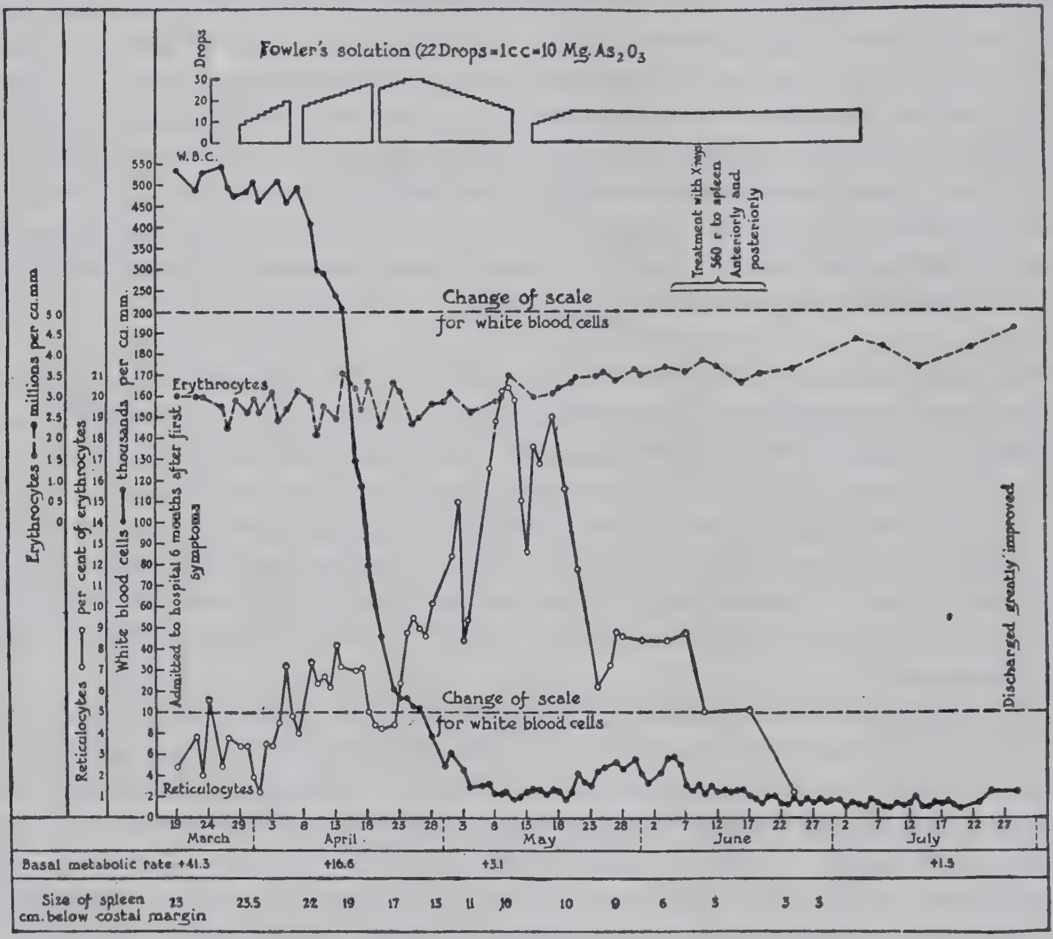


FIGURE 83. *The effect of solution of potassium arsenite (Fowler's Solution) in a case of chronic myelogenous leukemia.*

The drug causes a rapid fall to normal in the number of white blood cells, and decreases markedly both the absolute and relative numbers of immature leukocytes. The associated anemia is improved and the return of the hemoglobin and erythrocyte values to normal is accompanied by a reticulocytosis. The basal metabolic rate falls to normal and the size of the spleen is greatly reduced. (After Forkner, 1938.)

Arsenic depresses the formation of white blood cells, especially when their production is augmented. Only those compounds which release inorganic arsenic exert this effect. In the treatment of leukemia, arsenic was largely displaced by roentgen-ray therapy until its use was revived as a result of the studies of Forkner and Scott (1931) and Forkner (1932). Results with arsenic are especially good in the treatment of chronic myelogenous leukemia, particularly of the monocytic type. In fact, Forkner (1938) states in his monograph on leukemia that in his experience no case of chronic myelogenous leukemia failed to be strikingly benefited when treated with arsenic early in the course of the disease. The total number of white cells may be reduced by arsenic from several hundred thousand per cubic mm to numbers approximating normal, and immature leukocytes are decreased in number. Furthermore, the attending anemia is arrested and a reticulocytosis heralds a return of the red blood cell count toward normal. Cessation of medication results in a return of symptoms within a few weeks, but patients can often be maintained in therapeutic remission over long periods of time by chronic medication (Figure 83).

Forkner employs Fowler's Solution and his technic of administration is as follows: The initial dose is 0.3 cc, given three times daily for two days. This dose is then increased by 0.05 cc every other day until a dose level of 0.6 cc is reached. The dose is then further increased by 0.05 cc each day until toxic symptoms are pronounced or the leukocyte count approaches normal. Medication is now stopped for from two to five days and the individual dose is then decreased from the maximum by 0.05 cc per day until a maintenance level of 0.3 to 0.5 cc three times daily is reached. This dose is continued indefinitely. Success depends upon a strict therapeutic routine. Mild toxic symptoms must be disregarded. If the patient is unable to tolerate arsenic by mouth, it can be given by rectum or, if necessary, intravenously. The rectal dose employed is twice as great as the oral. For intravenous injection, a sterile dilute solution of potassium arsenite may be used. The dose is somewhat smaller than that used orally and is given only twice daily.

The advantages of arsenic over roentgen-ray therapy are the ease of administration, low cost, and the accuracy with which the dose can be controlled. Apparently, arsenic is effective in all cases which will respond to roentgen-ray therapy. Leukemia responding dramatically to arsenic should be suspected of being monocytic in type.

In the treatment of *psoriasis,* arsenic medication is only one of the innumerable procedures that have been tried. It is often employed, however, with fair results. Therapy is usually started with 0.1 cc of Fowler's solution three times daily. This dose is increased by 0.05 cc every other day until 0.5 cc is being taken at each dose. This level is maintained for a week or 10 days.

ANTIMONY

Historical. The element stibium (Sb, antimony) was probably known as early as 4000 B.C. It was used by the ancients as a medicine and a cosmetic. Several references to its cosmetic use may be found in the Bible. Both Dioscorides and Pliny discussed the use of antimony as a medicinal agent.

The derivative of the word antimony from stibium has been the subject of heated discussion. Etymologists consider that the Greek term "stimmi" was changed through the Arabic "isthimmi" and "athmud" to the Latin "antimonium." This is mentioned because there is an interesting account of the derivation of the word "antimony" which has a pharmacological background. During the time of Paracelsus, there was a group of practitioners known as "chemiatrists" who used chemical agents extensively in medicine. One of these was Johann Thölde who wrote under the pseudonym of a mythical monk, Basil Valentine. In his book "Triumphwagen Antimonii" published in Leipzig in 1602, Valentine describes his many experiments with stibium. He observed that pigs which had eaten food containing the mineral became very fat. It was of interest, therefore, to try the drug on some monks who had become emaciated as a result of prolonged fasting. He attempted the experiment, and as a result all the monks died. Hence, the name antimony, derived from the French "anti-moine," meaning antagonistic to monks. Berthelot, the great

French etymologist, calls this concept of the derivation of the word "etymologie puerile." He is undoubtedly correct, for the term antimony was used long before these experiments were supposed to have been performed. Nevertheless, this interesting story focuses attention on the toxicity of antimony, one of its most important properties.

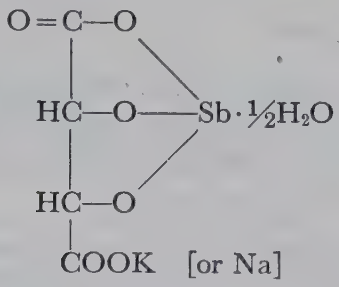
Antimony was widely used during the fifteenth and early sixteenth centuries and the medical profession of that time could be divided into two groups, depending upon their attitude toward this drug. Ultimately, the toxic actions of antimony became so obvious that the Faculty of Physicians of Paris decreed that no member should use or prescribe antimony. This ban was withdrawn after 100 years for a reason which is typical of medical thought of that time. In 1657, King Louis XIV became ill with typhoid fever. During the course of his illness many drugs were tried. Improvement occurred soon after a quack had administered antimony. This was sufficient to cause the withdrawal of the decree against the use of antimony and to assure the drug an enviable position in therapeutics until the nineteenth century, when it again fell into dispute.

Early in the twentieth century, antimony compounds were introduced as parasiticides. The use of antimony-containing drugs in the treatment of leishmaniasis has been termed one of the most significant advances in chemotherapy. Antimony compounds are also specific in combating certain worm infestations, notably schistosomiasis and filariasis. They have also been used in trypanosomiasis and lymphogranuloma inguinale.

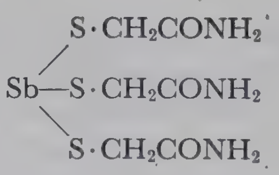
Chemistry and Preparations. The chemistry of antimony compounds is in many ways similar to that of the arsenicals. Both elements have two valences and form inorganic and organic complexes. The *inorganic compounds* of antimony can be dismissed, for they are never employed medicinally. Antimony oxide and antimony chloride have been given trials as therapeutic agents but their undesirable properties are too prominent.

The *organic compounds* of antimony can be divided into *trivalent* and *pentavalent* groups. Trivalent antimony compounds are more toxic than pentavalent, both with respect to the host and the parasite. Toxicity is probably related to the liberation of the trivalent inorganic antimony. Also there is a sharp distinction in the therapeutic applications of these two groups. The trivalent organic compounds are effective against all parasitic infestations which yield to antimony therapy. The pentavalent compounds, however, have comparatively little value in helminthiasis, and their use is restricted to the treatment of leishmaniasis.

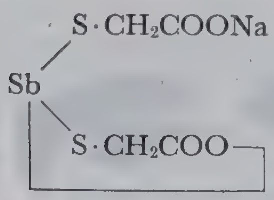
There are five *trivalent* organic antimony compounds of interest. Their names and formulas are as follows:



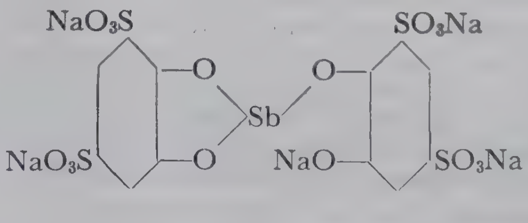
Antimony and Potassium [or Sodium] Tartrate (Tartar Emetic)



Antimony Thioglycollamide



Antimony Sodium Thioglycollate



Fuadin

Antimony and Potassium Tartrate (Tartar Emetic), U.S.P., B.P., consists of colorless, odorless transparent crystals or a white granular powder. It has a sweetish taste, and is soluble 1:12 in water. The drug is available in crystalline form, or in sterile solution in ampules for intravenous administration.

Antimony and Sodium Tartrate, B.P., is similar in physical characteristics to the potassium salt, but is more soluble in water.

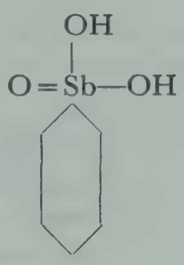
Antimony Sodium Thioglycollate, N.N.R., is a white or faintly pinkish, odorless powder, very soluble in water. It is marketed in ampules containing 10 or 20 cc of a 0.5 per cent solution.

Antimony Thioglycollamide, N.N.R., is a white, crystalline, odorless powder soluble in water to the extent of 1:200. It is marketed in ampules containing 10 or 20 cc of a 0.4 per cent solution.

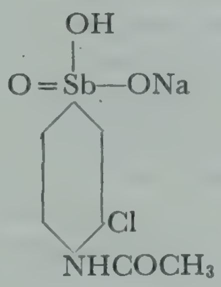
Fuadin, N.N.R., is available in ampules containing varying amounts of a 6.3 per cent solution of the drug (each cc represents 8.5 mgm of antimony).

Some investigators consider antimony and sodium tartrate less toxic than the corresponding potassium salt but, if pure preparations of both are used, it is probable that they are identical in action. The tartrate salts are too irritating to be given by mouth or intramuscularly and must be administered by intravenous injection. The other trivalent organic preparations were introduced to overcome these difficulties. They can be given intramuscularly and are said to be less toxic.

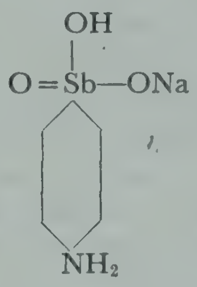
The organic *pentavalent* antimony compounds are derivatives of phenylstibinic acid. The names and structural formulas of several members of this group are as follows:



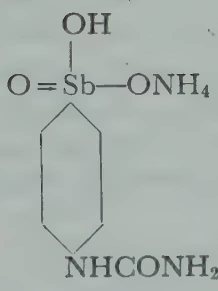
Phenyl Stibinic Acid



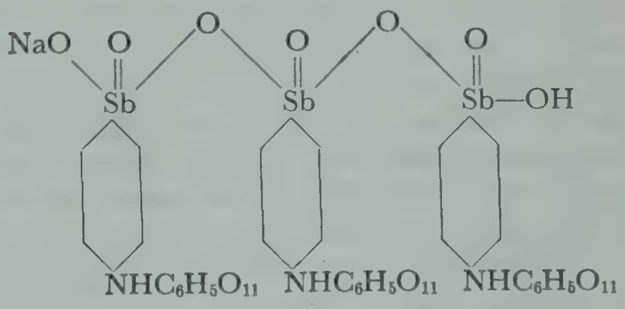
Stibosan



Stibamine



Urea Stibamine



Neostam

The pentavalent antimony compounds are infrequently used in the United States, the only available preparation being *Neostam.* It is marketed in ampules containing varying amounts from 0.05 to 1.0 gram. For injection, a four per cent solution in distilled water is employed. The pentavalent compounds can be given by intramuscular injection. Their advantage over the trivalent compounds will be discussed later.

Pharmacological Actions. The actions of antimony are closely related to those of arsenic.

Local. Upon local application, antimony is more caustic than arsenic. Compounds which liberate antimony are very irritating to the skin, and cause papular eruptions which later become vesicular and pustular. The lesions occur at the orifices of the cutaneous glands and it is probably at this site that the antimony can penetrate sufficiently to cause tissue reaction. Antimony compounds have been employed as irritants or rubefacients but they are much too toxic to be recommended for this purpose.

Emetic Action. The salts of antimony, notably the tartrates, are powerful emetics, chiefly by virtue of their irritant action on the gastro-intestinal mucosa. However, toxic doses are also emetic by virtue of a central action on the medulla.

If a subemetic dose is given, antimony has a nauseant and expectorant action. The salivary and bronchial glands are reflexly stimulated. Antimony is much too toxic to be used as an expectorant, especially if medication is continued for a period of time, as cumulative effects may occur. Nevertheless it is a component of many expectorant mixtures, chief among them being Compound Mixture of Opium and Glycyrrhiza, U.S.P., and Compound Syrup of Squill, N.F.

Antiprotozoan Action. The mechanism of action of antimony in protozoan infections is not understood. The drugs themselves are not directly parasiticidal and are not activated by contact with tissues or serum. Apparently some mechanism is involved in which antimony holds the infection in check and thus allows the defensive mechanisms of the body to operate more effectively.

Absorption and Excretion. Antimony compounds are slowly absorbed from the gastro-intestinal tract. This fact, coupled with the marked irritation which they produce, causes most of the antimony to be swept out of the bowel. Therefore, oral medication is never employed unless one is desirous of obtaining the nauseant or emetic effect. After intramuscular injection, the organic antimony compounds are rapidly absorbed. Both the trivalent and pentavalent compounds are excreted fairly rapidly, all of the antimony being eliminated largely through the kidneys within three days after the administration of a therapeutic dose.

Toxic Symptoms. The symptoms of acute and chronic antimony poisoning are so similar to those caused by arsenic that they need not be repeated. Antimony produces a more rapid irritation of the bowel and therefore emesis is prominent. The blood vessels are seriously affected and the shock syndrome is the outstanding feature of acute antimony poisoning. Improper medication with any of the antimony compounds may produce chronic poisoning. Antimony poisoning is rare in the United States because antimony is not widely used in medicine or industry. Treatment is the same as for arsenic poisoning.

There are certain untoward reactions attending the therapeutic use of antimony compounds which are of importance. These differ for the trivalent and pentavalent drugs. The following reactions may occur after administration of *trivalent compounds,* notably the tartrates: (1) Severe coughing, sometimes associated with vomiting, is likely to develop immediately after intravenous injection. (2) Pneumonia is not an unusual sequel to a therapeutic course of tartar emetic. It is definitely a reaction to the drug and not a complication of the disease being treated, because it is not encountered when pentavalent compounds are used. (3) Pains in the joints and muscles are common complications. They do not occur, however, until near the end of a therapeutic course. (4) Acute arthritis is a less common reaction. It generally involves the wrist, knee and ankle joints. (5) Marked bradycardia is a complication occasionally encountered late in a course of antimony therapy. It necessitates the discontinuation of medication Miscellaneous untoward reactions are headache, fainting and apnea.

The *pentavalent compounds* also produce side-effects. Vomiting and occasionally diarrhea may follow their injection. Emesis commonly occurs about twenty minutes after injection. Hepatitis is a rare but serious reaction and necessitates immediate cessation of medication. An anaphylactoid response, characterized by an urticarial rash, husky voice, and, in severe cases, collapse may be encountered after the sixth or seventh injection in a therapeutic course.

Therapeutic Uses of Antimony Compounds. The employment of trivalent organic antimony compounds in the treatment of schistosomiasis and filariasis is described in the chapter on anthelmintics. The remaining uses of antimony compounds are in the treatment of leishmaniasis, and lymphogranuloma inguinale. In the treatment of trypanosomiasis, antimony has largely been replaced by pentavalent organic arsenicals.

Kala azar. This is a tropical disease having a high incidence in countries bordering the Mediterranean Sea. It is caused by a protozoan, the *Leishmania donovani.* The disease is characterized by high fever, secondary anemia and severe leukopenia. The dusky hue often seen in individuals with the disease is the basis for the name kala azar, meaning "black sickness." The mortality rate in untreated cases is 90 per cent. Death usually results from secondary infection which cannot be readily combated due to the severe leukopenia. Either trivalent or pentavalent organic antimony compounds can be used in treating kala azar. The pentavalent compounds possess the following advantages. They are less toxic and therefore can be given in larger and fewer doses. They have also been found to be more effective, especially so in resistant cases. Lastly, there are fewer disagreeable side-actions accompanying their use. The one objection is their high cost. The treatment of kala azar is a complicated procedure and each preparation necessitates a different therapeutic routine. The details of therapy must be sought in texts on tropical diseases. Antimony compounds have also proved to be effective in the therapy of dermal and mucocutaneous leishmaniasis.

Lymphogranuloma Inguinale. In this disease, the trivalent organic antimony preparations have been employed. Antimony thioglycollamide may be administered intramuscularly or intravenously in courses of 15 to 25 injections given every second day. The single dose is 80 mgm dissolved in 20 cc of sterile water. Antimony sodium thioglycollate may also be given in similar courses but the interval between injections is three to four days. The single dose is 50 to 100 mgm dissolved in 10 to 20 cc of sterile water.

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CHAPTER 43

GOLD, SILVER, THALLIUM, SELENIUM, RADIOACTIVE ELEMENTS AND MISCELLANEOUS MINOR METALS

GOLD

At the time of Paracelsus, gold salts were highly regarded in the treatment of syphilis. Gold was later introduced for the treatment of tuberculosis, the rationale being based upon the bactericidal effect of gold salts on the tubercle bacillus *in vitro*. Gold, however, is not useful in tuberculosis because effective concentration cannot safely be obtained in the body. Gold salts are now seldom used clinically. They are sometimes effective in the treatment of lupus erythematosus, and this disease probably represents their only legitimate field of use.

Absorption, Distribution and Excretion. Soluble gold salts are poorly absorbed from the gastro-intestinal tract, the greater portion being precipitated and lost in the feces. After parenteral administration, the element gains access to the circulation and is partially stored and the remainder excreted. Seventy to 80 per cent of the excreted gold appears in the urine and the remainder in the feces. An appreciable amount is retained in the body for long periods of time and this is found in highest concentration in the kidneys, liver and skin. In therapy, gold salts are given by intravenous injection.

Toxic Reactions. Gold is one of the most toxic of therapeutic agents, and before it is employed the physician should be acquainted with the untoward reactions which accompany its use. Especially it must be emphasized that conservative estimates place the incidence of fatal reactions to gold therapy at one to three per cent (Hartfall and associates, 1937). The following reactions have been reported to occur after intravenous gold therapy:

Immediate Reactions. These are not common and include general malaise, headache, giddiness and vertigo, gastro-enteritis, acute pulmonary edema, laryngeal edema, asthma and cardiovascular collapse.

Focal Reactions. When used in the treatment of arthritis, gold is likely to cause an exacerbation of the pain and swelling in the involved joints.

Gastro-intestinal Reactions. These are frequent and consist of stomatitis, gastro-enteritis, vomiting, diarrhea and severe pain.

Renal and Hepatic Reactions. The urine is the main channel of excretion of gold salts and a high concentration of gold in the kidney results in toxic nephritis. Acute yellow atrophy of the liver and toxic hepatitis have also been reported.

Skin Reactions. These are the most frequent type of toxic reaction and may take any form. Urticarial, papular, vesicular, scarlatiniform and even exfoliative dermatitis may occur. Isolated cases of generalized pigmentation have also been recorded.

Hemopoietic Reactions. The bone marrow is especially sensitive to gold salts and all types of blood dyscrasias have been observed. The formation of platelets is especially disturbed and malignant thrombocytopenia has frequently been noted following gold therapy. Agranulocytosis and aplastic anemia are other toxic sequelae.

Nervous System Reactions. There are isolated case reports of peripheral neuritis following gold therapy.

Preparations. Although many organic gold-containing preparations are marketed, none probably is more effective or less toxic than *Gold Sodium Thiosulfate,* N.N.R., the inorganic gold salt most often employed. This is a white, crystalline, soluble salt which is almost neutral in solution. It is commonly marketed in powder form in ampules containing from 10 mgm to one gram.

Therapeutic Uses. The efficacy of gold therapy in *lupus erythematosus* seems to be definitely established. About one-third of the cases apparently are cured, another third improved, and the remainder unaffected. A conservative therapeutic routine starts with a dose of five mgm of gold sodium thiosulfate. Intravenous injections are made at weekly intervals and the dose is increased by five mgm each week to a maximum level of 50 mgm for women and 75 mgm for men. Untoward reactions call for immediate cessation of therapy, and a severe reaction contraindicates further use of the drug. A course consists of 10 or 15 weekly injections and a rest period of at least four weeks should intervene between courses. Patients with serious organic disorders should not be subjected to gold therapy.

There is an extensive literature on the use of gold salts in the treatment of *chronic arthritis.* Although favorable results have been reported, the spontaneous remissions which characterize this disease make it most difficult to attribute to gold any particular value in the therapy of arthritis. If gold is employed, the dosage and routine of administration are similar to that outlined above.

Although gold salts have been employed in many other conditions, they are of doubtful benefit and their toxicity does not warrant their use. There are numerous references to the use of colloidal gold preparations in the treatment of chronic pulmonary tuberculosis and cancer, but the available evidence fails to support the sanguine claims which are occasionally made. The indiscriminate use of gold salts can only be deplored.

SILVER

Silver was one of the earliest metals to be extracted. Although employed medicinally for several thousand years, silver came into prominence only after Paracelsus recommended its use for diseases of the nervous system. The basis for this suggestion was the relationship believed to exist between silver and the moon, and the belief that insane individuals ("lunatics") were under the influence of Luna, the moon-goddess. Until late in the nineteenth century, silver nitrate (lunar caustic) was still employed for the treatment of epilepsy.

At present, silver is employed only for its local actions. The silver ion precipitates protein and therefore is an effective *antiseptic* and *germicide.* It is used for this purpose either in the form of its inorganic salts, usually the nitrate, or in organic combination with protein. The antiseptic action of silver compounds is discussed in detail elsewhere (page 856). Silver is also combined with arsphenamine in a compound known as silver arsphenamine.

Systemic Actions. The systemic actions of silver are not extensive for the reason that silver is only slowly absorbed. Silver nitrate is readily soluble, but silver is rapidly precipitated in the body either as the chloride or proteinate. Therefore it is not possible to attain appreciable concentrations of the metal in the circulation. However, some silver does gain access to the body from mucous membranes and this is in large part retained.

Silver Poisoning. The ingestion of a soluble silver salt leads to a precipitation of the protoplasm of the mucosa of the digestive tract. If this is extensive, death may ensue from local trauma, hemorrhagic gastro-enteritis and shock. The fatal dose of silver nitrate is approximately 10 grams but recovery has been reported from much larger amounts. Treatment consists in the administration of sodium chloride and demulcents, and shock therapy.

Systemic symptoms have been observed only in experimental animals which have received parenteral injections of silver compounds. The silver ion seems to affect chiefly the medulla which it first stimulates and then depresses. Central vasomotor stimulation results in a rise in blood pressure. At the same time there is bradycardia due to central vagal stimulation. Death eventually results from respiratory depression.

Minute amounts of silver are ingested daily due to the wide use of this metal in dining utensils, and a portion of this is absorbed. It has been demonstrated that silver gradually accumulates in the body and in the latter decades of life reaches an appreciable concentration (Gaul and Staud, 1935). High concentrations of silver in the tissues, however, occur only after the careless administration of silver-containing medicinals. The absorbed silver is distributed in the connective tissue of the body, especially in the corium of the skin. Upon exposure to light, this silver turns dark in color and large amounts can impart to the skin a characteristic bluish pigmentation. This condition is known as *argyria.*

In the early nineteenth century, argyria was rather common because of the wide use of silver compounds in the treatment of nervous disorders. When this therapy was discarded, the incidence of argyria diminished markedly, but following the introduction of colloidal silver preparations as antiseptics and the use of silver arsphenamine, cases of argyria again increased in number.

Argyria can result either from industrial exposure to silver or from careless medication. Despite the claims of some manufacturers that colloidal silver preparations are harmless and can be taken orally with impunity, many cases of argyria have resulted from their use. Even the continued application of silver compounds to the mucous membranes of the nose may result in the swallowing of sufficient metal to cause cutaneous pigmentation (*see* Bryant, 1940). Silver arsphenamine has also been the cause of argyria.

The first sign of argyria may be a slate-blue "silver line" on the gingival margins adjacent to the teeth. Unfortunately, even if medication is immediately stopped upon its development, there is no assurance that further pigmentation will not occur. Especially those portions of the skin exposed to light become discolored and the hue may range from gray to one suggesting marked cyanosis. The famed "blue man" of Barnum and Bailey's Circus had argyria. No systemic effects accompany this pigmentation. The only injury sustained is a cosmetic one, but this remains for life. The silver pigment is soluble in sodium thiosulfate, but this agent is effective only in high concentration. Successful treatment of argyria is rare and requires the laborious intradermal injection of the entire area involved with six per cent sodium thiosulfate solution and one per cent potassium ferrocyanide solution (Stillians, 1937).

The sclera of the eye is particularly prone to manifest pigmentation from silver, the color ranging from a light bluish-gray to a brownish-black. The discoloration may occur after systemic or local administration and is often the first sign of argyria. If silver compounds are being applied locally, ulceration of the cornea increases the possibility of pigmentation. Experimentally it is possible to produce color changes in the eye within three weeks by the local instillation of 0.25 per cent silver nitrate. Clinical cases are on record in which pigmentation was observed within 10 days.

The problem of argyria and the pharmacology of silver have been extensively reviewed by Hill and Pillsbury (1939).

THALLIUM

Thallium is one of the most toxic of metals. Poisoning is caused by its therapeutic use as a depilatory, the accidental ingestion of thallium-containing rat poisons, or industrial exposure.

History. Thallium was discovered independently by Crookes (1862) and by Lamy (1862). The latter isolated the element in pure form and demonstrated its toxic properties. It was later introduced into therapy for the prevention of night sweats in tuberculosis, in which connection Combemale (1898) observed that thallium caused a rapid and complete loss of hair. The drug then came into clinical prominence as a depilatory and despite its marked toxicity its use for this purpose has continued sporadically and has led to the majority of poisonings.

Pharmacological Actions. All the actions of thallium may be classified as toxic. The metal is a powerful depilatory and loss of hair occurs two weeks after its systemic administration. The mechanism involved is unknown. It has been suggested that thallium has a powerful action on the sympathetic nervous system, greatly augmenting the normal response to stimulation (Dixon, 1927). Also, depilation by thallium often spares the strip of hair across the forehead which is said by some to receive its innervation directly from the cerebrospinal axis rather than from adrenergic nerves. These data provide the basis for the suggestion that the effect of the drug on the autonomic nervous system is the cause of the depilation. Upon histological examination, the hairs are seen to be split and the follicles enlarged. This action of thallium is reversible and, unless the administration of the drug is unduly prolonged, the normal growth of hair is resumed.

It has been claimed that thallium has a selective action on the endocrine glands, especially the gonads, thyroid and adrenals. Statements have been made that, accompanying thallium poisoning, ovarian function is markedly retarded and the basal metabolism falls. Cox and Rodgerson (1935), however, in experiments on rats could find no evidence that thallium had such a selective action.

The other important sites of thallium action are on the nervous system and circulation. In this respect, the element resembles arsenic. The nature of this action will be indicated in the discussion of thallium poisoning.

Absorption, Distribution and Excretion. Thallium is readily absorbed from the gastro-intestinal tract. It also gains access to the circulation when applied to the skin as a depilatory ointment. Thallium is partially stored in the body, being widely distributed to all organs. It is excreted both by the kidney and the intestine.

Thallium Poisoning. The incidence of thallium poisoning can be appreciated from the review of Munch (1934) who found 778 cases reported in the literature, 46 (six per cent) of which were fatal. When one considers that numerous cases have probably remained undiagnosed or unreported, these figures become even more significant.

Symptoms of acute thallium poisoning become evident within 12 to 24 hours after the ingestion of a toxic amount. They are mainly referable to the nervous system and the alimentary tract. The gastro-intestinal symptoms are not due to the local action of the drug but are probably the result of a toxic effect on the capillaries after absorption. The patient suffers from severe paroxysmal abdominal pain, vomiting and diarrhea. Hemorrhage and desquamation of the mucosa occur. Stomatitis is frequent and may be ulcerative. A gingival line similar to that observed in poisoning from certain other heavy metals may be observed. In chronic poisoning, the gastro-intestinal symptoms are not severe.

The first evidence of nervous system disturbance is paresthesia of the hands and feet, and the condition progresses to a frank peripheral polyneuritis. The legs are involved more often than the arms. Lesions are not confined to the peripheral nerves. Retrobulbar neuritis is a common feature of chronic thallium poisoning and the damage may be permanent in character. Ptosis, strabismus, mydriasis, and facial palsies also occur. In severe acute poisoning, symptoms include delirium, convulsions and even death from respiratory failure. In chronic poisoning, central necrosis of the liver and damage to the renal glomeruli and tubules are complicating features. Also there are skin changes characterized by various types of eruptions and a keratinization of the epithelium. Ecchymoses and petechiae are also observed.

Treatment. In treating acute poisoning, sodium thiosulfate has been recommended but there is no proof of its efficacy. A daily injection of 20 cc of a three per cent aqueous solution has been employed. The therapy outlined for arsenic poisoning is probably more efficacious. In chronic poisoning, removal from continued exposure is essential, and symptomatic therapy is instituted. Thallium intoxication should be suspected in every case of unexplained polyneuritis and its possibility should not be dismissed until diligent questioning has ruled out the use of the element in depilatory preparations. Recovery is slow and incomplete after long exposure.

Therapeutic Applications. Thallium acetate has been employed as a depilatory in the treatment of ringworm of the scalp in children. The drug was at one time considered safe to administer to children before the age of puberty, but even when thus restricted it has often caused poisoning. Thallium is a most unnecessary and dangerous drug, and its use can only be deplored. The effective dose is too close to the toxic. The conditions for which thallium has been employed are not dangerous and readily yield to other measures. The drug has no official status.

Thallium has been incorporated in commercial depilatory preparations, one of which was found to contain more than five per cent thallium. These depilatory creams have caused many cases of poisoning.

SELENIUM

Selenium is an element, chemically related to sulfur, which has long been recognized as toxic. It was only of academic interest, however, until it was appreciated that selenium is present in high concentrations in plants grown on soils rich in this element and that animals feeding on such plants can become poisoned.

Selenium poisoning in animals was formerly called "alkali disease." It was first described in 1856 by Madison, an army surgeon stationed at Fort Randall located in what is now South Dakota. Frequent periodic reports of this disease were made from South Dakota, Wyoming, North Dakota, Kansas, Montana, Nebraska, Colorado and New Mexico. The symptoms were not definitely ascribed to the consumption of selenium-contaminated grain until the relationship was demonstrated by Franke (1934).

Inasmuch as selenium contaminates grains and vegetables consumed by human beings as well as livestock, the public health aspects of this element are also being actively studied. In addition, the use of selenium in industry has increased markedly and the United States Public Health Service, aware of the dangers of the wide industrial use of selenium, is extensively investigating this phase of its toxicology.

Absorption, Distribution and Excretion. Selenium, fed as pure salts or in the form of contaminated grain in which it is probably present in organic combination, is readily absorbed from the gastro-intestinal tract. Solutions of inorganic salts also gain access to the blood from parenteral sites of administration. Selenium fumes, dust and hydrogen selenide are also absorbed from the respiratory membranes.

After absorption, selenium is transported by the blood. The greater portion is in the corpuscles, probably in organic combination with protein (Dudley, 1936). It soon leaves the circulation, however, and is widely deposited, the highest concentrations being found in the liver, kidneys and spleen (Smith, Westfall and Stohlman, 1938). Appreciable amounts are also found in the hoofs of animals. Following the removal of selenium from the diet of experimental animals, the major portion of the stored element is excreted within two weeks, although a trace remains after a month.

Selenium is excreted by the kidneys and intestinal tract. Fifty to 80 per cent appears in the urine and 18 per cent in the feces (Smith, Westfall and Stohlman, 1937). Some of it is converted into the volatile methyl selenate, which has an odor of stale horseradish and is detectable on the breath.

Natural Selenium Poisoning. This is observed in animals grazing on contaminated grains. Its incidence is sufficiently high to assume economic importance. The animals affected are cattle, horses, swine, sheep and chickens. Acutely poisoned animals stray from the herd and show signs of impaired vision. The eyelids are edematous and there is profuse lacrimation. The coat is roughened. The ends of the long bones are eroded and there is difficulty in walking. The appetite is depraved and there is evidence of severe abdominal pain. Death results from respiratory failure. Chronic poisoning is mainly characterized by stunting of growth and inability to reproduce. The hoof elongates and assumes shapes so bizarre that animals often have to graze on their knees. It has been suggested that this deformity results from the replacement of sulfur, which is present in high concentration in the hoof, with selenium. Also there is a marked loss of body hair. In affected chickens, the eggs are either sterile or produce a high percentage of monstrosities. Autopsies on animals succumbing to selenium poisoning reveal hemorrhagic gastro-enteritis, marked liver damage, degeneration of the renal tubules, atrophic spleens, myocardial atrophy, hydropericardium, congested lungs with thickened alveolar walls, and a high incidence of ascites.

Experimental Selenium Poisoning. The symptoms noted after intravenous administration of selenium are congestion, hemorrhage and edema of the lungs, muscular weakness, labored respiration and asphyxial convulsions. Death occurs in from 18 to 24 hours, but it may be delayed six to nine days (Smith, Stohlman, and Lillie, 1937).

Chronic experimental selenium poisoning differs little from that which occurs naturally. There is no doubt that the actions of selenium are cumulative, for the daily administration of as little as 10 per cent of the acute toxic dose will result in death in about three months. There is no evidence for the development of tolerance (Smith, Stohlman and Lillie, 1937). Pathological examination of chronically poisoned animals reveals lesions similar to those described. In addition, the blood-forming organs are affected. The bone marrow is hypoplastic and there is a generalized myeloid metaplasia.

Selenium as an Industrial Hazard. Although there have been few reports of selenium poisoning in industry, the huge increase in the industrial consumption of this element has led to the appreciation that selenium may become an industrial hazard (Dudley, 1938). Selenium is readily absorbed from the lungs. Dudley and Miller (1937) have determined that guinea pigs exposed to hydrogen selenide in the concentration of 0.02 mgm per liter of air for only 60 minutes succumb within 25 days. Higher concentrations breathed for shorter periods of time are equally toxic. In the few cases of industrial poisoning which have been reported, the symptoms were pallor, gastro-intestinal disturbances, a garlicky odor of the breath and perspiration, irritation of the nose and throat, coating of the tongue, metallic taste in the mouth, and nervousness (Dudley, 1938).

Selenium oxychloride, a liquid with unique properties, may also assume toxicological significance. It is a powerful vesicant. One one-hundredth of a cc applied to the skin of a rabbit causes death in less than 24 hours. As little as 0.005 cc applied to the skin of a man produces a painful ulceration which does not heal for several weeks.

Selenium as a Public Health Hazard. The high concentration of selenium in the soil of certain geographical regions has raised the question of the possibility of human selenium intoxication. Smith and Westfall (1937) investigated the inhabitants of highly seleniferous areas of South Dakota and Nebraska and found that many individuals excrete a significant amount of selenium in their urine (20 to 198 micrograms per 100 cc). There was a high incidence of gastro-intestinal symptoms and a few cases of liver disorder which were believed to be associated with selenium ingestion. Meat, eggs, milk and vegetables proved to be the most constant source of selenium.

RADIOACTIVE METALS

The important radioactive metals are *radium, thorium,* and *uranium.* These elements are continually decaying and diminishing in quantity as a result of the explosion of their atoms. In the course of this process, radium gives off the following, in the indicated proportions: alpha particles (helium nuclei), 92 per cent, beta rays (electrons), 3.2 per cent, and gamma rays, 4.8 per cent. All of these are ionizing radiations and produce biological effects which are believed to be secondary to this ionization. These radiations are destructive to tissue, especially to certain rapidly proliferating cells, and under carefully controlled conditions they are of therapeutic value.

It is only the gamma rays which are clinically effective for these have a high capacity to penetrate tissue. They are similar in character to roentgen rays and the toxic effects which result from the excessive *external applications* of radium are similar to those obtained from roentgen rays. These consist of dermatitis, radium burns, skin cancer, the acute constitutional symptoms of radiotoxemia and chronic constitutional symptoms such as blood dyscrasias, hypotension, sterility, intestinal ulceration, tissue fibrosis, etc.

The use of radioactive compounds in industry and their employment in quack medicinals have caused *radium poisoning.* This condition results from the ingestion, injection or inhalation of radioactive compounds such as radium and mesothorium and must not be confused with the toxic syndrome already described. When radioactive compounds are absorbed, the alpha particles, which have poor penetrative capacity and are ineffective in radiotherapy, gain direct access to the tissues where they exert their deleterious effects. These alpha particles are comparatively large and are discharged at a velocity of 12,000 to 18,000 miles per second. Thus they have a tremendous kinetic energy and an ionizing power 10,000 times greater than the gamma rays. Although they can penetrate tissue only to the depth of a few hundredths of a millimeter, once they gain access to the body and are widely distributed, this poor penetrative capacity is no impediment to their toxic action.

Absorption, Fate and Excretion. Radium is absorbed, distributed and excreted in a manner analogous to lead. Its behavior in the body can be studied accurately because the physical method for the detection of radium, based upon a measurement of the intensity of the discharge of gamma rays, is a thousand times more sensitive than the most accurate of chemical procedures. Martland (1938) has described the course which radium takes in the body and the following facts have been established. When radium salts are ingested orally, only a small proportion is absorbed. Of that which is absorbed, 65 to 98 per cent is excreted within a four day period, 10 per cent in the urine and the remainder in the feces. However, that radium which is retained after this initial period of excretion becomes firmly fixed and it has been estimated that approximately 45 years are required to reduce the amount of retained radium by one-half. The distribution of radium in the body is exactly the same as that of lead. After absorption it is phagocytozed by the reticulo-endothelial system and following a brief sojourn in the body tissues, especially in the liver and spleen, it enters the skeleton where it is retained. After inhalation, a large amount can be detected in the lungs. The toxic action of radium is due to the destructive effects on bone.

Radium Poisoning. Most cases of poisoning have resulted from the industrial use of radium-containing luminous paints. Before the toxic properties of this element were fully appreciated, workers engaged in painting the figures on luminous watch dials tipped their brushes by moistening them in their mouths. As a result, they ingested appreciable amounts of radioactive substances. Industrial hygiene has eliminated this hazard and radium poisoning is now a rare occurrence. However, a danger still exists in the mining of radioactive ores and in the use of radioactive medicinals.

There may be a latent period of several years between the exposure to radium and the onset of toxic symptoms, depending upon the amount of metal in the body. The toxic dose is exceedingly small. Bone changes have been associated with a total body radium content of only 0.001 mgm. The skeletal effects are first reflected in the blood picture. There is megaloblastic erythropoiesis with accompanying leukopenia. The pathological changes in the bone ultimately consist of a replacement of the marrow by fibroblastic tissue, and the development of osteogenic sarcomata. There is also decalcification and softening of the bone, and deformities and spontaneous fractures are common. Terminally, an aplastic anemia occurs.

There is no curative treatment for radium poisoning. Aub and coworkers (1938) showed that those procedures which mobilize calcium from bone will also mobilize radium. However, the two elements are dissolved from osseous tissue in the proportion in which they are present. Therefore, despite intense decalcification, much of the radium remains deposited. Other than temporary amelioration of symptoms by blood transfusions and supportive measures, little can be accomplished.

Therapeutic Uses. A consideration of the clinical uses of radium is beyond the scope of the present discussion. Numerous claims have been made for the therapeutic efficacy of the systemic administration of radioactive compounds. This procedure has been employed in many diseases, but no acceptable proof exists that it is in the least beneficial. Usually, radioactive substances are administered in the form of "radon" charged water. *Radon* is the gaseous element which remains after radium has lost four units of its atomic weight. Its radioactivity is of short duration and this is probably the reason why few toxic sequelae have resulted from this type of therapy.

Thorium dioxide has been introduced for the purpose of roentgen visualization of blood vessels, especially of the liver and spleen. It is injected intravenously and the maximum doses employed have a gamma ray equivalent of one to three micrograms of radium. Mesothorium remains radioactive over long periods of time and patients who receive injections of this compound still retain 50 per cent of the original activity one year after administration. The excretion of radioactive elements can still be easily demonstrated after seven years (Stenstrom and Vigness, 1940). Martland (1938) emphasized the toxic potentialities of such a procedure and pointed out that it may take years for the toxic effects of these radioactive substances to become manifest. Despite the fact that their employment is unassociated with immediate symptoms, they are potential hazards and should be used only with a full appreciation of the danger involved. For example, a patient coming to autopsy five years after receiving 75 cc of colloidal thorium oxide showed significant fibrotic changes of the liver, spleen, lymph nodes and femoral arteries believed to be due to the radioactivity. The liver contained approximately 27 per cent of the original gamma ray activity (Jacobson and Rosenbaum, 1938). Reeves and Stuck (1938) have reviewed the literature pertaining to the use of radioactive thorium compounds as diagnostic aids.

Radioactive Isotopes. It is possible to form radioactive isotopes of the common elements by bombarding them with deutrons in a cyclotron. Many elements have been thus transformed and their half-life of radioactivity varies, depending upon the element, from two minutes to many months. Such elements emit beta or gamma rays, or both, or positrons. Few therapeutic applications have yet been made of radioactive isotopes. However, they are proving to be valuable research tools because elements tagged in this manner can be followed through the body accurately. Chemically their behavior is the same as that of the original elements. Inasmuch as the rate at which these substances lose their radioactivity is accurately known, their distribution and fate in the body can be closely followed by sensitive quantitative physical methods.

ALUMINUM

Aluminum is used in therapeutics only for its local effects. The soluble salts of aluminum precipitate protein and have an astringent and antiseptic action. Insoluble compounds such as aluminum hydroxide are effective adsorbents and have a special field of usefulness as gastric antacids.

Although aluminum is never employed for its systemic actions, these are of practical importance because of the wide use of aluminum cooking utensils.

Absorption, Distribution and Excretion. It is not possible to state with any degree of certainty the extent to which aluminum is absorbed. Despite the fact that this problem has occupied the attention of many investigators, results are not in accord. Mackenzie (1931, 1932) was unable to detect appreciable absorption of aluminum from the gastro-intestinal tract of the rat or rabbit. On the other hand, Underhill and Peterman (1929) demonstrated absorption in the dog, and Lewis (1931) showed the same for man. It can be stated, however, that absorption is limited.

Aluminum absorbed from the gastro-intestinal tract or injected intravenously leaves the circulation rapidly and is partially stored and partially excreted. The organs which contain the highest amounts of the metal are the liver, kidney, spleen, thyroid and brain. Excretion is by way of the urine and bile.

Toxicity. Despite the fact that some aluminum apparently gains access to the circulation, there is no evidence that this is harmful in amounts even much greater than normally encountered. Mackenzie (1932) could observe no effect of feeding large amounts of aluminum on growth or reproduction in rats. Examinations of workers exposed to aluminum dust in industry reveal no characteristic occupational disease. Neither are any untoward systemic effects observed in individuals receiving orally large amounts of insoluble aluminum compounds, despite the fact that appreciable quantities are probably rendered soluble by the acid gastric contents. In view of these facts, it is fallacious to believe that toxic amounts of aluminum can be obtained from cooking utensils. The amount of aluminum dissolved in the preparation of food is so small as almost to escape detection. Much larger concentrations are found in certain uncooked foods (Underhill and Peterman, 1929).

There have been isolated reports of death in human beings following the ingestion of large amounts of soluble aluminum compounds. The symptoms are due to the local action on the gastro-intestinal mucosa and do not differ from those produced by other protein precipitants.

The single toxic parenteral dose of aluminum chloride or sulfate in experimental animals is high, being over 5.0 grams per kilo (Underhill and Peterman, 1929). Death occurs in from two to 11 days. The outstanding pathological changes are renal tubular damage and central necrosis of the liver.

Preparations and Therapeutic Uses. These are discussed under astringents and gastric antacids.

ZINC

Zinc is employed in therapeutics solely for its local actions. Certain salts of zinc are valuable astringents and antiseptics.

Although the systemic actions of zinc have no therapeutic application, the metal is seemingly an essential element in nutrition. Zinc is a constituent of most foods and is necessary for the normal growth and development of both plants and animals. Todd, Elvehjem and Hart (1934) demonstrated that rats fed on a diet low in zinc did not grow as rapidly as control animals fed the same diet with added zinc. In addition, the experimental group suffered from loss of hair. In a further study, Hove, Elvehjem and Hart (1937) produced evidence to show that a defect in intestinal absorption might account for the symptoms observed.

An excess of zinc in the diet will also lead to untoward reactions. Sutton and Nelson (1937) showed that, although rats fed diets containing 0.1 per cent of zinc remained symptom-free, if the concentration was increased to 0.5 per cent, reproduction was affected. Animals ingesting 1.0 per cent zinc failed to grow or reproduce and evidenced severe anemia, and some of the rats succumbed. Removal of the zinc led to a rapid amelioration of symptoms.

In the animal body, the highest concentration of zinc is found in the pancreas. Scott and Fisher (1935) reported that zinc is invariably present in all samples of crystalline insulin. In fact, it is impossible to crystallize insulin in the absence of zinc or other closely related metals. Zinc also will enhance the stability of protamine insulin suspensions and greatly prolong the duration of action of this insulin complex. Scott and Fisher (1938) fed zinc to cats over long periods in an attempt to relate this metal to insulin production. They observed that large amounts were deposited in the pancreas, which became fibrotic and reduced in size. The total insulin content, however, remained unchanged.

It has also been found that zinc will increase the activity of certain hormonal preparations such as anterior pituitary extract. However, here it is believed that the metal does no more than retard the rate of absorption by its astringent effect and thus prolong the duration of action of the extract.

Zinc Poisoning. Poisoning from zinc results either from the oral ingestion of its salts or the inhalation of particles of zinc oxide. Symptoms differ depending upon the route of access. After oral ingestion of soluble salts, there is a local action on the gastro-intestinal tract due to the precipitation of the protoplasm of the mucosa. Nausea, vomiting, diarrhea and abdominal pain are the common symptoms. With controlled doses of zinc, it is possible to produce emesis without tissue damage and consequently zinc sulfate has been employed to some extent as an emetic.

Sufficient zinc can be dissolved from utensils made of galvanized iron to cause zinc poisoning, if their contents are acid in reaction. Callender and Gentzkow (1937) report accidental zinc poisoning in a large number of soldiers who drank limeade prepared in galvanized iron cans. The inhalation of zinc dust results in a syndrome formerly known as "brassfounders' ague" but now called "metal fume fever." The outstanding features are chills, fever, and marked leukocytosis. The fever soon subsides and within 24 hours the patient has recovered. It has been postulated that zinc precipitates the proteins of the bronchial epithelium and that the symptoms result from absorption of the toxic protein products.

The existence of chronic zinc poisoning is disputed. Batchelor, Fehnel, Thomson, and Drinker (1926) studied workers exposed to zinc over a long period and although an abnormally high content of zinc was found in the blood and urine, no signs of chronic poisoning were observed. These investigators believe that symptoms ascribed to chronic exposure to zinc are due to other metallic impurities of a more toxic nature, such as lead and arsenic.

Parenteral Administration. The parenteral administration of large amounts of zinc to experimental animals results in serious symptoms. The metal is partially excreted by the intestinal tract and bile and this results in vomiting, diarrhea, and hemorrhagic enteritis. There is also depression of the central nervous system and tremors and paralysis of the extremities. The blood pressure is only terminally affected. After the oral administration of zinc compounds, the rate of absorption is too slow for this syndrome to occur.

Preparations and Therapeutic Applications. The preparations and therapeutic uses of the astringent and antiseptic zinc compounds are presented elsewhere (page 860).

MANGANESE

Manganese is a metal widely distributed in nature, being found in all plant and animal tissues. It is one of the trace elements apparently essential for both plant and animal nutrition. It is believed that the function of manganese in plants may be concerned with oxygen metabolism. The rôle which it plays in mammalian physiology is not known.

Manganese is seldom used in therapeutics. Potassium permanganate, a powerful oxidizing agent, is employed as an antiseptic and chemical antidote. Aside from this, the main pharmacological interest in manganese arises from the fact that the metal is the cause of industrial poisoning.

Physiological Rôle of Manganese. Animals fed diets low in manganese develop certain well-defined abnormalities. Kemmerer, Elvehjem, and Hart (1931) reported retarded growth. Orent and McCollum (1931) observed that manganese deficiency results in loss of testicular function in male rats and the production of abnormal offspring in females. Gallup and Norris (1939) showed manganese to be essential for normal bone development in chicks, the absence of the element leading to osteoporosis. In view of the fact that bones of mammals contain appreciable amounts of manganese, they believe that manganese may play a similar rôle in higher forms. Manganese has also been studied in regard to its ability to stimulate hematopoiesis in animals made anemic by milk diets. Although it has been well established that combinations of iron and copper are effective in stimulating red blood cell production in such nutritional anemias, the possibility of replacing copper with manganese has been debated. Present evidence indicates, however, that copper is perhaps more specific in this regard.

Absorption, Distribution and Excretion. Manganese is only slowly absorbed from the gastro-intestinal tract and much of it escapes in the feces. That which is absorbed rapidly leaves the blood stream and is stored mainly in the liver and kidneys. The metal is excreted largely into the colon and the bile. A small portion escapes by way of the urine.

Manganese Poisoning. Aside from experimental poisoning in animals, this condition has been reported only in connection with industrial exposure to manganese. In the United States, the element is employed in making manganese steel and dry batteries. The metal is absorbed through the lungs as a result of the inhalation of manganese dust or fumes. The clinical picture of poisoning often simulates a progressive hepatolenticular degeneration, similar to that seen in Wilson's disease. Manganese is unique in that it injures in a highly selective manner a fairly discrete portion of the central nervous system. The neurological syndrome resembles in some respects that characteristic of Parkinson's disease. There is a mask-like expression of the face and the voice is low and monotonous; intention tremor of varying degree is almost always present; the patients commonly complain of muscle pains which increase after exertion; muscular rigidity results in a spastic gait, and retropulsion and propulsion occur; the tendon reflexes are increased; there is ankle and patellar clonus; emotional disturbances are not marked although some individuals may show involuntary laughing or crying. In addition to neurological injury, many cases of manganese poisoning manifest liver cirrhosis. Both the hepatic and nervous system lesions seen clinically can be produced experimentally in animals with toxic amounts of manganese (*see* von Oettingen, 1935). The patient is disabled, but life is not directly endangered.

Manganese poisoning runs a progressive course which cannot be arrested. There is no specific therapy for manganese poisoning.

Preparations and Uses. Manganese preparations have been used for many skin disorders and infections but the results are not promising (*see* Sullivan, 1940; Report of the Council, 1940). The antiseptic uses of potassium and zinc permanganate are described elsewhere (page 851).

NICKEL

Nickel is a metal of no therapeutic importance, but it is often the cause of an annoying dermatitis known as nickel eczema. This is frequently observed in workers engaged in nickel plating and may also result from the wearing of nickel-plated objects such as wrist watches and eyeglass mountings. In industrial poisoning, the skin eruption starts on the arms, and if exposure continues it may spread to involve other portions of the body. The lesion consists of an edematous exanthem with miliary vesicles. It is accompanied by intense itching. The occurrence of nickel eczema is favored by sweating. Also there is evidence that the initial attack sensitizes the skin to the metal so that subsequent exposure results in a more rapid and severe progression of symptoms (Foster and Ball, 1935).

Nickel carbonyl is another source of industrial poisoning. This is a gas formed by the reaction of metallic nickel and carbon monoxide, the basis of the Mond process for the purification of nickel. Inhalation of nickel carbonyl results in the deposition of nickel in a finely divided state on the epithelial surfaces of the respiratory tract. Absorption slowly occurs and causes severe systemic reactions characterized by edema of the lung and extensive capillary damage. Multiple hemorrhages result and are especially severe in the brain, lungs and adrenals. Upon inhalation of this toxic gas, the initial symptom is a feeling of malaise. This is relieved by fresh air but in 12 to 36 hours the systemic action is manifest and death occurs within four to 11 days. (*See* the review of Brandes, 1934.)

The parenteral injection of nickel compounds in experimental animals results in widespread capillary damage with a marked fall in blood pressure, toxic effects on the intestines, kidneys and adrenals, and central nervous system stimulation characterized by muscle tremors and tetany, followed by paralysis.

COBALT

Cobalt is similar to nickel in its pharmacological properties. The compounds of cobalt are little used in industry and few cases of cobalt poisoning have been reported. It has been observed that the cobalt miners of Schneeberg are prone to develop primary carcinoma of the lung but this may be due to pneumoconiosis.

An interesting property of cobalt is the stimulation of the hematopoietic system which follows the parenteral administration of very small amounts. Polycythemia has been observed in all species of animals studied. There is an increase of approximately 20 per cent in both the erythrocyte count and hemoglobin. The mechanism of cobalt polycythemia was extensively investigated by Orten (1936). He believes it to be the direct result of a stimulation of the bone marrow, for polycythemia is preceded by reticulocytosis. There is an increase rather than a decrease in the bilirubin content of the serum and this is taken by Orten as evidence that polycythemia cannot be due to a decrease in the rate of destruction of cells. Cobalt apparently does not stimulate leukocyte production.

In a study of the trace elements necessary for the treatment of milk anemia of rats, Underwood and Elvehjem (1938) found that cobalt was not essential for the regeneration of hemoglobin.

TELLURIUM

Tellurium is a relatively unimportant element from a pharmacological standpoint. Its compounds are not employed in therapeutics, and the use of tellurium in industry is so limited that the industrial hazard is not great.

Tellurium salts are not readily absorbed from the gastro-intestinal tract. For the most part, they are converted into an insoluble form and excreted. After parenteral administration, tellurium compounds are converted into *methyl telluride,* a gaseous substance with a pronounced garlic odor. This is excreted in the exhaled air, the urine and feces.

After parenteral administration in experimental animals, tellurium causes hemorrhagic gastro-enteritis, muscle tremors and paralysis, respiratory arrest, asphyxial convulsions and death.

Industrial Poisoning. There have been only a few cases of industrial poisoning from tellurium. The metal occurs as an impurity in lead and constitutes a hazard in the electrolytic refining of lead. The route of entrance is through the lungs. The symptoms which have been observed are dryness of the mouth, a metallic taste and garlic breath, inhibition of sweating, itching and scaling of the skin, anorexia, nausea and vomiting, and somnolence.

TIN

Tin is a relatively innocuous metal as evidenced by the absence of reports of harmful effects from this element despite its wide use. Absorption of tin from the gastro-intestinal tract of man is very limited. The parenteral administration of tin to experimental animals results in a stimulation and subsequent depression of the central nervous system. Diarrhea and vomiting are also noted.

Tin tetrachloride is used in weighting silk and there have been isolated instances of toxic effects resulting from the inhalation of this compound. It is irritating to the respiratory passages in concentrations of 8.5 parts per million.

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SECTION XII

DRUGS ACTING LOCALLY ON THE SKIN AND MUCOUS MEMBRANES

CHAPTER 44

DEMULCENTS, EMOLLIENTS, PROTECTIVES, ADSORBENTS, IRRITANTS AND ASTRINGENTS

There are a large number of drugs which act locally in a purely mechanical or physical manner. Although they possess both therapeutic and pharmaceutical usefulness, their pharmacological properties warrant only the briefest discussion inasmuch as their actions are confined to the site of application. These actions are adequately described by the definitive names which are applied to the groups into which the drugs can be classified, namely *demulcents, emollients, protectives* and *adsorbents.* Two other types of drugs which act primarily at the site of application but which have a chemical rather than a physical basis of action are the *irritants* and *astringents.*

DEMULCENTS

The demulcents comprise a group of compounds of high molecular weight which form aqueous solutions having demulcent and protective properties. Chemically, most of the members of the group are gums, mucilages or starches. When applied locally to irritated or abraded tissues, the demulcents tend to coat the surface and by mechanical means protect the underlying cells from stimuli resulting from contact with air or irritants in the environment. The demulcents are applied to the skin in the form of lotions, poultices, or wet dressings, to the gastro-intestinal tract in the form of demulcent drinks or enemas and to the throat in the form of lozenges or gargles. The demulcents also have valuable pharmaceutical properties. They mask the taste of obnoxious drugs, and solutions of demulcents are often used as vehicles for this purpose. They are also employed for the purpose of forming stable emulsions or suspensions of drugs immiscible or insoluble in aqueous vehicles. The following are the more important of the demulcents and their outstanding properties.

Acacia (*Gum Arabic*), U.S.P., B.P., is the dried gummy exudation from the stems and branches of *Acacia Senegal.* In its ground form it consists of a white powder which is readily soluble in water, but insoluble in alcohol. *Mucilage of Acacia,* U.S.P., consists of a 35 per cent solution with 0.1 per cent sodium benzoate added as a preservative (B.P., 40 per cent acacia in chloroform water). Acacia is employed chiefly in making pharmaceutical preparations, the colloidal solution which it forms being an excellent vehicle for suspensions or emulsions of drugs (page 1319). It is also incorporated in lozenges. The uses of solution of acacia as a diuretic (page 633) and as a substitute for plasma (page 588) are discussed elsewhere.

Tragacanth (*Gum Tragacanth*), U.S.P., B.P., is the dried gummy exudation from *Astragalus gummifer.* In its powdered form it consists of white angular fragments. Tragacanth, in contact with fifty volumes of water, swells to form a cloudy gelatinous mass. It is used as a demulcent base for cutaneous medication, often in the form of *Mucilage of Tragacanth,* U.S.P., a mixture of tragacanth (six per cent) and glycerin (18 per cent) in water (B.P., tragacanth in chloroform water). (*See* also page 1319.)

Glycyrrhiza (*Licorice Root*), U.S.P., B.P., is the dried rhizome and roots of *Glycyrrhiza glabra.* In its ground form it consists of a brownish-yellow powder. Preparations obtained from the crude drug include the fluidextract, extract and elixir. Glycyrrhiza is employed locally as a demulcent and internally as a mild expectorant. It is also widely favored as a vehicle for expectorant drugs and is useful in masking the flavor of ill-tasting medicines. For this purpose, *Syrup of Glycyrrhiza* (N.F.) and *Fluidextract of Glycyrrhiza* (U.S.P.) are often used.

Althea (*Marsh Mallow Root*), U.S.P., is the dried root of *Althaea officinalis.* The drug forms mucilaginous demulcent solutions which offer relief in the symptomatic treatment of coughs and inflammations of mucous membranes.

Chondrus (*Irish Moss*), N.F., is the dried bleached plant of *Chondrus crispus,* a form of seaweed. It contains up to 80 per cent pectin. In three per cent aqueous solution it forms a jelly, *Mucilage of Chondrus,* N.F., which is a valuable demulcent vehicle for drugs. It has also been employed internally in the treatment of diarrhea. Chondrus has an unwarranted reputation as a nutriment.

Glycerin. Glycerin, because of its wide solubility, may be classified both as a demulcent and an emollient. *Glycerin* (*Glycerol*), U.S.P., B.P., is a trihydroxyalcohol, $CH_2OHCHOHCH_2OH$, and consists of a clear, colorless, syrupy liquid having a sweet taste. Glycerin is extensively employed as a vehicle for many drugs applied to the skin. Diluted with rose water it is an effective lotion for chapped and roughened hands. In combination with starch it forms a jelly base known as *Glycerite of Starch,* U.S.P., B.P. In addition to being a valuable vehicle, the preparation is often employed as a lubricant, as is also *Glycerite of Boroglycerin,* U.S.P., B.P., a solution of boric acid in glycerin. There are several other official medicated glycerin solutions, among which may be mentioned *Glycerite of Tannic Acid,* U.S.P., B.P., *Glycerite of Phenol,* N.F., B.P., *Glycerin of Alum,* B.P., *Glycerin of Borax,* B.P., and *Glycerite of Iodine and Zinc Iodide,* N.F.

Glycerin absorbs water and therefore in high concentration is somewhat dehydrating and irritating to exposed tissue. Concentrated solutions, for this reason, are slowly bactericidal. The irritant action of glycerin accounts for its efficacy in promoting evacuation of the bowel when used rectally in the form of a suppository. Glycerite of tannin is used as a swab for sore throats.

When given orally, glycerin is readily absorbed and serves as a source of energy. It may be employed as a sweetening agent or vehicle in place of syrups.

EMOLLIENTS

Emollients are fats, oils or fat-soluble substances which are used for their local action on the skin, and occasionally on the mucous membranes. They are employed as protectives, as agents for softening or rendering the skin more pliable, but chiefly as vehicles for more active drugs. As vehicles they are useful for drugs having either local or systemic actions. When systemic effects are desired from drugs applied locally in emollient vehicles, the medicated ointment should be thoroughly rubbed into the skin to insure adequate absorption through the sebaceous glands. Mercury inunction, for example, is employed in this manner in syphilotherapy. The following are the commonly employed emollients.

Vegetable Oils. Official vegetable oils are *Olive Oil,* U.S.P., B.P.; *Cottonseed Oil,* U.S.P.; *Corn Oil,* U.S.P.; *Expressed Almond Oil,* U.S.P.; *Linseed Oil,* U.S.P.; *Theobroma Oil* (*Cacao Butter, Cocoa Butter*), U.S.P., B.P. With the exception of the last named preparation, all are fluids. When taken internally, they act as mild cathartics and protectives for the gastro-intestinal tract in cases of corrosive poisoning. When applied externally, they are emollient to the skin or mucous membrane. They also form the vehicles for many drugs which are injected in oily solution or suspension. Theobroma oil is a solid which melts at body temperatures. It is widely used as a suppository and ointment base.

Animal Fats. The outstanding animal fats of pharmacological interest are *Lard,* U.S.P., B.P., *Wool Fat,* (*Anhydrous Lanolin*), U.S.P., B.P., and *Prepared Suet,* U.S.P., B.P. These are all solids and are used principally as bases for ointments. Lard is frequently employed in the form of *Benzoinated Lard,* U.S.P., B.P. Wool fat is usually employed mixed with 25 to 30 per cent water (*Hydrous Wool Fat, Lanolin*), U.S.P., B.P., in which form it possesses more desirable physical properties, being quite cohesive and adherent.

Hydrocarbons. The important emollient hydrocarbons are *Paraffin,* U.S.P., B.P., *Petrolatum,* U.S.P. (*Yellow Soft Paraffin,* B.P.), *White Petrolatum,* U.S.P. (*White Soft Paraffin,* B.P) and *Liquid Petrolatum,* U.S.P. (*Liquid Paraffin,* B.P.). Solid petrolatum is more commonly known as vaseline. Paraffin is mainly used in ointments to raise their melting points. Petrolatum is a common ointment base and also is employed as an emollient and lubricant. Drugs are not absorbed through the skin from a petrolatum base. Liquid petrolatum is used as a vehicle, especially for drugs to be applied to the nasal mucous membranes, and internally as a cathartic.

Waxes. *White Wax* (*Bleached Beeswax*), U.S.P., B.P., and *Yellow Wax* (*Beeswax, Yellow Beeswax*), U.S.P., B.P., are employed to harden ointment bases. A base composed of lard hardened with wax is known as a *cerate. Spermaceti,* U.S.P., is a waxy substance obtained from the head of the sperm whale.

An emollient widely employed is *Rose Water Ointment,* U.S.P. Most of the commercial cold creams are modifications of this basic preparation. It consists essentially of spermaceti, white wax, expressed almond oil, rose water and oil of rose.

PROTECTIVES AND ADSORBENTS

Certain insoluble and chemically inert substances in a very fine state of subdivision are used locally as mechanical *protectives.* They act mainly by preventing friction and by absorbing moisture. Dusting powders are the outstanding agents in this category. *Purified Talc,* U.S.P., consists chiefly of magnesium silicate. *Lycopodium,* U.S.P., consists of the spores of *Lycopodium clavatum.* The compound is a unique dusting powder in that it resists wetting by water. It also absorbs oily substances, having in itself a high oil content. Other compounds employed as dusting powders include *zinc oxide, zinc stearate, boric acid, starch, chalk* and *insoluble salts of bismuth.*

A number of chemically inert powders are used internally as protectives and adsorbents. Their protective action is employed in the treatment of ulcerations of the bowel and for this purpose the heavier powders, such as the insoluble salts of bismuth, are preferred. These are as follows: *Bismuth Subnitrate,* U.S.P., *Bismuth Subcarbonate,* U.S.P., B.P., and *Bismuth Subgallate,* U.S.P. The compounds supposedly coat the crater of the ulcer and in this manner offer mechanical protection. The insoluble bismuth salts are also used for the treatment of *enteritis, diarrhea, dysentery* and *ulcerative colitis.* They are given suspended in water in a dose of two to five grams at intervals of two to four hours.

Many powders possess adsorptive properties and as a group are known as the *adsorbents.* Unfortunately adsorption is not a specific action and when compounds having significant adsorptive capacity are given by mouth, nutriments and enzymes as well as noxious substances present in the bowel are adsorbed to their surface. Outstanding adsorbents are *Activated Charcoal,* U.S.P., a fine, black, odorless and tasteless powder, and *Kaolin,* N.F., B.P., a clay consisting chiefly of hydrated aluminum silicate. Another adsorbent is aluminum hydroxide which adsorbs hydrochloric acid so efficiently that it is discussed under the gastric antacids (page 787).

The adsorbents are used for treating various intestinal disorders, and their therapeutic applications have been reviewed by Emery (1937). Kaolin has long been recommended in China for the treatment of *diarrhea* and is employed in modern medicine for the same purpose. It is effective if the diarrhea is caused by an agent capable of being adsorbed, as for example, in cases of *food poisoning* or infection with organisms causing *dysentery.* Kaolin is given suspended in water in doses of from 50 to 100 grams at three hour intervals until the desired effect is obtained. Kaolin has also been employed in the treatment of *chronic ulcerative colitis* for the purpose of adsorbing bacteria and toxins in the colon, but it is doubtful whether appreciable activity is retained by the time the drug reaches the large bowel. In the treatment of *diverticulitis* of the colon, kaolin and barium sulfate have been employed for the purpose of filling the diverticula with an inert substance, but Emery (1937) questions the efficacy of the procedure and warns of the danger of an obstruction or perforation.

In the treatment of *intestinal fermentation,* charcoal and kaolin have been employed for the purpose of adsorbing gases, toxins and bacteria. It is doubtful whether adsorbents can materially decrease the gaseous contents of a distended bowel. In its dry state, however, charcoal is one of the most effective adsorbent of gases and forms the chief protection in modern gas masks. Charcoal has a limited usefulness as an antidote in cases of *poisoning,* adsorbing the toxic substance and thus retarding its absorption until gastric lavage can be performed.

IRRITANTS

The irritants are drugs which act locally on cutaneous tissue to produce "inflammation." They can best be described as agents which injure protoplasm, and the reactions in tissues which follow the local application of irritant substances are merely the defense mechanisms operating to protect the tissue. The first response to local irritation is an increased circulation to the injured part, and the basic mechanism for the localized vasodilatation is an axon reflex. Attending the vasodilatation there is the subjective feeling of comfort, warmth and sometimes itching. Localized hyperesthesia also occurs. Mild irritation causes little more than circulatory changes in the skin, although if continued for a sufficiently long period, subsequent desquamation may occur. Drugs which effect only reactive hyperemia are known as *rubefacients.*

If the irritant action progresses, however, the capillaries dilate widely and become more permeable. Plasma escapes into the extracellular spaces, fluid collects under the epidermis and blisters are formed. At first these are small and discrete but later coalesce. Drugs capable of causing this degree of irritation are known as *vesicants.* Actually little distinction can be drawn between the rubefacients and vesicants, the degree of irritation usually being determined by the concentration of the drug employed and the time during which it is allowed to act.

There is another type of irritant which readily penetrates into the orifices of the sebaceous glands, acting locally at these sites rather than diffusely over the surface of the skin. This leads to the formation of small multiple abscesses which, if the irritant action proceeds, may become confluent. Such a drug is called a *pustulant.* The pustulants have few therapeutic indications.

Irritants have been employed in therapy on an empirical basis for many centuries and are still rather widely used, especially by the laity. In general they are utilized for two purposes, to increase the circulation to a limited area of the body or to relieve pain.

The area affected by the action of an irritant is not limited to the portion of skin directly exposed to the drug. When an irritant agent is being used for other than its local effects it is commonly referred to as a *counterirritant.* The mechanism of action of counterirritation is a dual one, as follows: The afferent nerve fibers from the skin synapse in the cerebrospinal axis with efferent vasomotor fibers to internal organs. Thus the increased circulation of the skin has its counterpart in deeper integumental structures and in viscera innervated from the same level of the central nervous system. Furthermore, when pain arises from an internal organ it is believed that sensory impulses simultaneously coming from the skin, as a result of the action of an irritant, may either alter the character of the visceral sensations or more probably occupy the final common pathway to the partial or complete exclusion of the impulses arising from the viscera. For example, pain arising from intestinal spasm might be relieved by the use of a rubefacient either through the salutary effect of an increased circulation to the spastic bowel or by the blocking of visceral afferent impulses.

Local irritation can also reflexly stimulate the central nervous system. Thus a painful stimulus may reflexly stimulate medullary centers and cause increases in respiratory rate and blood pressure. Thus, subcutaneous injection of an irritant substance (ether, camphor, etc.) is sometimes employed in resuscitation.

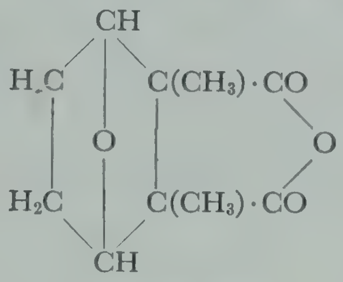
Drugs are the least useful means available for producing hyperemia, irritation and counterirritation. Physical measures are employed much more frequently than chemical agents. Heat is often the rubefacient of choice, the hot water bottle or pad, hot wet packs and the heat lamp being simple means for applying heat. Short wave diathermy is a more modern and effective method for producing localized hyperemia. Localized circulatory changes can be produced by still other methods than chemical irritation or physical therapy. Parasympathomimetic drugs may now be employed by iontophoresis for the purpose of increasing the blood flow in a discrete area.

Preparations. Many drugs have an irritant action when applied locally, but this constitutes such a minor part of their pharmacological properties that their applications as irritants are discussed elsewhere. Included in this category are *chloroform, camphor, eucalyptol, ether, aconite, turpentine,* and *methyl salicylate* (*see* Index). Two drugs which are used chiefly as irritants are *mustard and cantharides.*

Black Mustard, U.S.P. This is the dried ripe seed of *Brassica nigra* or *juncea,* or of varieties of these species. The preparation yields on contact with moisture not less than 0.6 per cent of volatile oil of mustard, consisting primarily of *allyl isothiocyanate* (C_3H_5NCS) which is the active irritant. The oil is formed as the result of a reaction between a glycoside and an enzyme in the presence of water. *Volatile Oil of Mustard* is also a U.S.P. preparation but is seldom prescribed. Mustard is usually employed in powdered form. It is sometimes used internally as an emetic but its chief use is as an irritant.

Mustard Plaster, U.S.P., consists of a uniform mixture of powdered black mustard (deprived of its fixed oil) and a solution of rubber spread on paper, cotton cloth or other suitable backing material. Each 100 square centimeters of spread plaster contains not less than 2.5 grams of mustard deprived of its fixed oil. A mustard plaster is first thoroughly moistened with *tepid* water and then applied to the skin. The water must not be hot or the enzyme which liberates the volatile oil will be inactivated. Within five minutes it produces a decided warmth and reddening of the skin. The irritant action proceeds to vesication in time and an undiluted plaster should not remain in contact with the skin longer than 15 to 30 minutes. Rubefaction persists for from 24 to 48 hours.

Cantharides (*Spanish Flies, Russian Flies*), U.S.P. This consists of the dried insects *Cantharis vesicatoria.* The active irritant of this crude drug is *cantharidin* (official in the B.P.), a white crystalline substance, sparingly soluble in water but more soluble in organic solvents and having the following chemical composition:



Cantharidin

Cantharidin has a rubefacient and vesicant action on the skin but is said to cause less pain than mustard because the compound does not penetrate tissue as readily. The drug also has an intensely irritant action on mucous membranes and when taken orally causes vomiting, purging, abdominal pain and shock. The drug is absorbed from the gastro-intestinal tract and to a limited extent from the skin, and irritates the urinary tract during the course of its excretion. It is more irritant in an acid than in an alkaline urine. Irritation of the bladder causes a constant desire to urinate and the presence of the drug in the urethra results in priapism. Cantharides therefore is popularly known as an aphrodisiac, and indeed was used as such by the early Greeks and Romans, not to mention its use by the laity today. If large amounts of the drug are absorbed, extensive renal damage occurs. Cantharides was formerly employed internally for various diseases of the urinary tract but now is seldom used. However, it still enjoys some favor as a rubefacient. *Cantharides Cerate* (*Blistering Cerate*), U.S.P., consists of 35 per cent cantharides in a cerate base and is employed in the preparation of *Cantharides Plaster,* U.S.P., which contains 0.1 gram on each square centimeter of plaster. The B.P. contains a similar plaster containing 0.2 per cent cantharidin. Plaster of cantharides should remain in contact with the skin for approximately four hours. Certainly safer methods of obtaining the same results are available and no great loss would be suffered if cantharides were no longer obtainable. The drug should never be employed if renal disease is present.

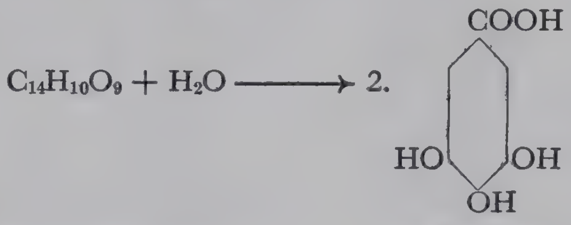
Therapeutic Uses. Irritants have been employed in the treatment of a variety of diseases which in the past included pleurisy, pneumonia, neuralgia, rheumatism, tuberculosis, arthritis and innumerable other conditions. The development of antisera, antitoxins and chemotherapeutic agents for the treatment of specific infectious diseases and the rapid strides in physical therapy have made the use of skin irritants almost obsolete. Nevertheless, the old-fashioned mustard plaster will probably hold its place for many years to come, and the turpentine stupe has brought relief to many patients with postoperative ileus when more elaborate and less benign measures have failed. Heat lamps and dry or moist hot packs, however, are usually as effective as medicated plasters, solutions, etc., and are particularly indicated in localized cutaneous infections or cellulitis, myositis, arthritis, bursitis, tenosynovitis and similar integumental afflictions. They also give some measure of relief in renal colic, pain due to intestinal spasm, etc.

ASTRINGENTS

Astringents are drugs which have a precipitant action on proteins and which are used locally to produce this effect. The compounds do not possess great penetrability, their precipitant action is relatively weak, and therefore only the surface of cells is affected. Consequently, the permeability of the cell membrane is greatly reduced but the cell itself remains viable. Many of the germicidal protein precipitants possess an astringent action in high dilutions. As examples may be cited the salts of silver and mercury. Other metallic ions, such as those of zinc and aluminum, are primarily astringent. The astringent actions of the heavy metals are considered in connection with their other pharmacological properties (*see* Index). Of the vegetable astringents, by far the most important is tannic acid.

Tannic Acid

Source and Chemistry. A variety of tannic acids is found in nature and chemically they are anhydrides of different hydroxy benzoic acids. The acid commonly referred to as tannic acid is *gallotannic acid,* the anhydride of *gallic acid.* It is usually obtained from *nutgall,* an excrescence on the young twigs of various species of *Quercus* (oaks). The chemical relationship between gallic acid and tannic acid is expressed in the following formula:



Gallotannic Acid Gallic Acid

The tannic acids are obtained from glycosides which consist of several molecules of a tannic acid in combination with glucose. The glycosides yielding tannic acid are correctly classified as the *tannins,* but the term tannin is ordinarily used as a synonym for tannic acid. There are many crude plant preparations which possess astringent actions by virtue of their content of tannins. Several have an official status, but none is of sufficient importance to warrant description.

Pharmacological Actions. The only important pharmacological property of tannic acid is its activity as a precipitant. Tannic acid not only precipitates protein but also forms insoluble complexes with many of the heavy metals, alkaloids and glycosides. Thus tannic acid is of some value as a chemical antidote in poisoning. The precipitant action of tannic acid on protein is markedly affected by pH, protein tannate being redissolved in a medium which is strongly acid or alkaline.

Tannic acid has little action on the intact skin, but exerts its full effects in the absence of a protective epidermis. When applied to abraded tissue, it precipitates a protein film which acts as a mechanical protective, an action which finds unique application in the treatment of burns. The familiar process of the tanning of animal hides is an example of the commercial use of the precipitant action of tannic acid on proteins. Formerly, inks were largely made by the reaction of tannic acid with ferric salts, an illustration of the reaction of the compound with heavy metals. The high reactivity of the tannins contained in crude drug preparations represents a common source of incompatibility encountered in the compounding of prescriptions.

Actions on the Gastro-intestinal Tract. Tannic acid exerts an astringent action on the mucous membranes of the gastro-intestinal tract. When taken orally its solutions have a harsh "astringent" taste and constrict the mucous membranes of the mouth and throat. Therefore, when oral therapy with tannic acid is employed, the drug should always be administered in encapsulated form. In the stomach, tannic acid exerts a precipitant action on the mucous membranes. If large amounts of drug dissolve in the stomach, gastric irritation, nausea and vomiting result. For this reason, various relatively insoluble derivatives of tannic acid have been introduced into therapy.

In the duodenum, the pH is favorable for the precipitant action of tannic acid but the drug becomes progressively less effective as the intestinal contents become more alkaline. The pellicle formed by the precipitation of the protein of mucus and of the protoplasm of the surface cells of the intestinal tract acts as a mechanical protective. Secretory activity and the transudation of fluids are retarded, and if irritants are present in the bowel, their effects on the intestinal mucosa are diminished. As a result, tannic acid has a constipating action and this is of therapeutic value in the treatment of diarrhea.

Absorption, Fate and Excretion. Tannic acid is not absorbed as such from the gastro-intestinal tract but rather is hydrolyzed to gallic acid in the course of its passage along the bowel. Gallic acid is not astringent, is readily absorbed and apparently is oxidized in the body, for little is detectable in the urine.

Preparations. *Tannic Acid* (*Tannin, Gallotannic Acid*), U.S.P., B.P., consists of an amorphous powder, glistening scales or spongy masses varying in color from yellowish-white to light brown. The compound is very soluble in water, glycerin or alcohol. Solutions of tannic acid should be freshly prepared unless protected by a preservative. Official preparations of tannic acid are *Ointment of Tannic Acid,* U.S.P., B.P. (20 per cent in an ointment base), and *Glycerite of Tannic Acid,* U.S.P. (20 per cent tannic acid and one per cent sodium citrate in glycerin) (*Glycerin of Tannic Acid,* B.P., 15 per cent in glycerin). The B.P. also includes an official suppository and lozenge of tannic acid.

The fact that tannic acid is highly soluble leads to an undesired degree of action in the stomach when the drug is given orally, and a complete loss of action occurs before the terminal portions of the bowel are reached. Therefore, several relatively insoluble derivatives of tannic acid have been introduced in order that the action on the gastric mucosa be diminished and that the drugs, as they slowly dissolve, exert an astringent action along the length of the intestinal tract. *Acetyltannic Acid* (*Diacetyltannic Acid, Tannyl Acetate, Acetannin*), U.S.P., is a product obtained by the acetylation of tannic acid. It is a yellowish-white or grayish-white powder which darkens upon exposure to air. Acetyltannic acid is only slightly soluble in water and in the gastric juice. It is not astringent until hydrolyzed. In the intestinal tract, the compound is slowly hydrolyzed to tannic acid and supposedly acts at all levels of the bowel. *Albumin Tannate (Albutannin)*, U.S.P., is a compound of albumin and tannic acid. It consists of a yellowish-white powder which it almost insoluble in water but decomposes in alkaline solutions. Albumin tannate is hydrolyzed by the digestive enzymes of the stomach and intestines to yield tannic acid. The compound presumably has a greater action on the gastric and duodenal mucosae than does acetyltannic acid. *Protan,* N.N.R., is a chemical combination of tannic acid and casein. The compound is more readily soluble and more easily decomposed by alkaline solutions than either of the preparations mentioned, and is also readily dissolved by the gastric juice.

Therapeutic Uses. Tannic acid is used internally for the symptomatic treatment of *diarrhea,* especially in children. The insoluble derivatives are the preparations of choice for oral administration inasmuch as they have the least action on the stomach and the most extensive action on the intestinal tract. The dose for children ranges between 0.2 and 1.0 gram every few hours. Too much reliance should not be placed on this type of therapy but rather attention should be focused on combating the etiology of the disorder and on maintaining the volume and composition of the extracellular fluids (Chapter 32). In bacillary, amebic or flagellate *dysentery* and in *chronic ulcerative colitis,* an enema of two per cent tannic acid solution may help to control the symptoms.

As a *chemical antidote in poisoning,* tannic acid is of some value for the precipitation in the stomach of numerous alkaloids, glycosides and heavy metals. Important alkaloids which are not precipitated by tannic acid are cocaine, nicotine, physostigmine, atropine and morphine. Neither is the drug an effective precipitant for arsenic, antimony and mercury. When using tannic acid as an antidote it is conveniently administered in the form of strong tea after which the stomach should be thoroughly lavaged because the tannates readily redissolve to liberate the poison.

Tannic acid is used for topical cutaneous application as an astringent in the treatment of such conditions as *bed sores, weeping ulcers, eczema-dermatitis,* etc. It is conveniently applied in the form of the official ointment or as a spray of a five or 10 per cent solution.

Treatment of Burns. Tannic acid finds its chief application in the local treatment of burns.

Before discussing the use of tannic acid in the treatment of burns, it is pertinent briefly to review the pathological physiology of burns in order better to understand the rationale of the current therapeutic procedures. The most obvious effect of a burn is the localized injury to tissue. This results in capillary dilatation at the site of injury and as a consequence large amounts of plasma may escape from the confines of the circulation. If the burned surface is extensive, the amount of fluid lost in this manner may seriously embarrass the circulation. There is a reduction of blood volume due to the loss of plasma and the concentration of formed elements in the blood therefore rises, leading to an increased viscosity of the circulating fluid. As a result of an inefficient circulation, tissues become anoxic, further capillary dilatation occurs, and shock results. Attention was first called by Underhill and coworkers to the significance of the loss of plasma following severe burns and this factor has since been emphasized by many investigators (Underhill and coworkers, 1923; Blalock, 1931; Harkins, 1935, 1938). A major objective in the therapy of burns, therefore, centers around the replacement of lost fluids and electrolytes in order to prevent shock and to maintain an adequate circulation.

Despite proper therapy designed to maintain the normal composition of the body fluids, patients with severe burns may run a progressively downhill course following a brief period of apparent improvement. To account for this clinical fact it has been proposed that some toxin is absorbed into the systemic circulation from the site of the burn. The toxin theory as an explanation for the fatal outcome of severe burns is an old one, and many substances have been proposed as the causative agent. Underhill and coworkers (1930) discounted the toxin theory on the basis of their observations that substances such as strychnine were not absorbed to an appreciable extent when applied to the site of a burn. However, the theory was again revived when it became apparent that, despite adequate replacement of fluids, the course of the illness in many patients was unfavorable. Aldrich (1933, 1937) has proposed that secondary infection with subsequent toxemia plays a major rôle in the clinical course of burned patients, and he believes the most common invading organism is the *beta* hemolytic streptococcus. As a result of this concept, he introduced a routine of treatment with germicidal dyes. This type of therapy has much in its favor and many proponents.

Although all investigators are agreed that burned tissue is very likely to become infected and that all precautions should be taken to avoid this occurrence, many remain unconvinced that infection is the cause of toxemia (Wilson and coworkers, 1937; McClure, 1939). Rather the belief exists that some toxin is formed in the burned tissue which gains access to the circulation. The organ most vulnerable to the toxic agent is apparently the liver, and hepatitis of varying degree accompanies the acute toxemia which may follow a severe burn.

The therapy of burns centers around the following objectives: (1) the prevention of circulatory failure and shock; (2) the prevention or treatment of secondary infection; (3) the prevention of toxin formation; and (4) the institution of supportive measures designed to aid the patient in coping with the deleterious effects of any toxin which may be formed.

Shock due to burns may be immediate or secondary in onset. Immediate shock is probably due to pain and fright; secondary shock, to fluid loss. Aldrich (1937) recommends that prophylactic treatment be administered for secondary shock and advises that all patients with a burn of one-eighth or more of the body surface be given shock therapy whether shock is present or not. This includes adequate sedation and the intravenous administration of saline and glucose solutions. If large amounts of body fluid have been lost from the burned area and the plasma volume is thereby greatly reduced and the hematocrit increased, the problem of treatment is more difficult. The injection of a large volume of saline or glucose solution will lead to a marked reduction in the concentration of plasma protein. Ideal therapy, therefore, consists in transfusion with plasma. If this is impossible, withdrawal of blood by venesection and its replacement by transfusion with normally hydrated blood is an alternative but this is considered too radical a procedure by Blackfield and Goldman (1939) and one to be condemned. Saline-free fluids should not be forced too strenuously by mouth because the replacement of the isotonic plasma lost through the injured capillaries with hypotonic fluid by mouth leads to a decrease in the concentration of the electrolytes of the extracellular fluids and a shift of water into the cells. The symptoms of water intoxication may then develop (page 581). Flavored saline drinks may be employed to quench thirst. Adequate hydration helps to maintain normal renal function and this is essential in order to assure the elimination of metabolic end-products and perhaps aid in the excretion of any toxin which may be absorbed.

Another important phase of the therapy of burns centers about the local treatment of the injured tissue. Although some clinicians minimize the importance of local therapy (Trusler and coworkers, 1939), the majority give it careful attention. The outstanding drug for this purpose is tannic acid. The use of tannic acid in the local treatment of burns was introduced by Davidson (1925). The rationale was to prevent absorption of toxins by converting the injured protein into inert tannates. Whether this purpose is actually accomplished cannot be stated, but the formation of a firm eschar by the precipitated proteins is undoubtedly a factor in protecting the tissue from bacterial infection and preventing the extensive loss of fluids. The patient is first scrupulously prepared using aseptic technic, the burned area being cleansed and the blebs incised. Tannic acid is applied in the form of a spray of a five or 10 per cent freshly prepared solution Fantus (1937) has proposed the use of a 10 per cent solution of tannic acid in Ringer's solution, containing 0.1 per cent salicylic acid as a preservative. This obviates the necessity of making a fresh solution of the drug before each use. By several applications of tannic acid, a thick eschar is formed within 15 to 18 hours.

Tannic acid is not actively germicidal, and therefore various substitutes have been proposed in order more readily to combat the dangers of infection. Bettman (1935, 1937) introduced the technic of combining tannic acid with silver nitrate. Immediately after the initial application of a five per cent tannic acid solution, the burned area is sprayed with a 10 per cent silver nitrate solution. Advantages claimed for this method are that a thin and pliable eschar which remains dry is immediately formed, that silver nitrate is a very powerful germicide against all organisms and that the burned area remains sterile. Also, the immediate formation of the eschar prevents fluid loss, lessens the likelihood of infection, adds greatly to the comfort of the patient, and reduces nursing care. No untoward reactions have been reported from this type of therapy and apparently there is no danger from argyria.

As an alternative of tannic acid, Aldrich (1933, 1937) prefers the germicidal dyes. The agent originally employed was gentian violet. Gentian violet combines with the proteins of the protoplasm of the injured cells to form a firm but thin and pliable eschar. It is claimed that tissues treated with the dye heal readily, that less skin grafting is necessary and that the scar tissue which does form is fairly soft and does not contract markedly. A one per cent aqueous solution of gentian violet is employed and is administered by spray at two hour intervals until the eschar is formed (a matter of approximately eight hours). Spraying is continued two or three times daily until healing is complete. If areas become softened from underlying infection, they are opened and the exposed tissue is again sprayed. The peripheral margins of the eschar are kept trimmed to the edge of the healed area.

Gentian violet has the disadvantage that it is effective only against Gram-positive organisms. Therefore, Aldrich (1937) adopted the use of a dye combination consisting of acriviolet (a loose chemical combination of gentian violet and acriflavine) and brilliant green. The details of treatment are the same as those cited. Blackfield and Goldman (1939) have devised a therapeutic regimen which combines the use of tannic acid, silver nitrate and gentian violet. There are many who favor the local treatment of burns with the germicidal dyes.

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CHAPTER 45

GASTRIC ANTACIDS AND DIGESTANTS

GASTRIC ANTACIDS

Gastric antacids are drugs which lower the acidity of the gastric contents. They are employed by physicians chiefly in the treatment of hyperchlorhydria and peptic ulcer, and by the laity in the form of widely advertised nostrums for the self-medication of any symptom which seems to originate in the stomach.

Perhaps no group of drugs is used with less discrimination than the gastric antacids. They are looked upon as innocuous substances, the actions of which are confined to the stomach. As a result of wide advertising, the belief has been fostered in the minds of both the public and the physician that man is constantly fighting a battle against acidity, and should he, in an unguarded moment, digress from the alkaline side, the results would be catastrophic. Actually, the indiscriminate use of antacids may lead to severe uncompensated alkalosis, a condition which is too infrequently recognized despite the fact that its incidence is in all probability high.

Classification. The gastric antacids may be classified in two ways, and both classifications yield valuable information as to their pharmacological properties. A division can be made between *systemic* and *non-systemic antacids.* A systemic antacid is one that is soluble and readily absorbed, and which is capable of producing changes in the pH of the blood and the symptoms of alkalosis. This group of compounds, even if administered in doses which only partially neutralize the gastric contents, disturbs the acid-base balance of the body fluids and imposes upon the kidney the burden of readjustment. The non-systemic antacids form compounds which are not absorbed and the members of the group are much less prone to cause alkalosis.

The gastric antacids may also be classified on the basis of the manner in which they decrease the acidity of the gastric contents, by *chemical reaction* or by *physical adsorption.* Many colloidal substances are effective antacids in that they bind hydrochloric acid by adsorption. Basic compounds react chemically with the acid in the stomach to form neutral salts.

Chemical Changes Incident to Gastric Secretion. In order to appreciate the difference in action between a systemic and non-systemic antacid, it is necessary to understand the chemical changes which occur in the body as a result of the secretion of acid and alkaline fluids into the gastro-intestinal tract.

The hydrochloric acid of the stomach is formed from chloride obtained from the extracellular fluids, where chloride is present in the concentration of approximately 100 mEq per liter in the form of the neutral sodium salt. Chloride has little function in maintaining the pH of the body fluids, being subservient in this respect to the other important inorganic anion, bicarbonate. It is largely the ratio of sodium bicarbonate to carbonic acid which determines the pH of the blood.

The secretion of hydrochloric acid into the stomach decreases the chloride concentration of the extracellular fluids. The sodium which is released combines with bicarbonate ion, a ready supply of which is available from the carbon dioxide produced in the metabolic processes. As a result of this ionic exchange, the concentration of sodium in the blood remains unchanged, whereas the chloride is diminished in amount and the bicarbonate is increased. In the event that the gastric contents are lost from the body, as by vomiting, an alkalosis results for which the kidney compensates if supplied with the proper constituents (page 591). Normally, however, the gastric contents pass into the intestine where they react with the pancreatic and biliary secretions. Whereas the gastric juice is acid and contains large amounts of chloride and no bicarbonate, the intestinal secretions contain a higher bicarbonate and lower chloride content than do the extracellular body fluids and are more alkaline in reaction. As a result of their secretion, the bicarbonate content of the blood is reduced and this compensates for the changes produced by the secretion of acid. The gastric juice reacts with the intestinal fluids to form neutral salts in the following manner:

$$HCl + NaHCO_3 \longrightarrow NaCl + H_2O + CO_2$$

The carbon dioxide is absorbed by the circulation and excreted by the lungs. The sodium chloride is also absorbed, and the composition of the blood is restored to normal (Figure

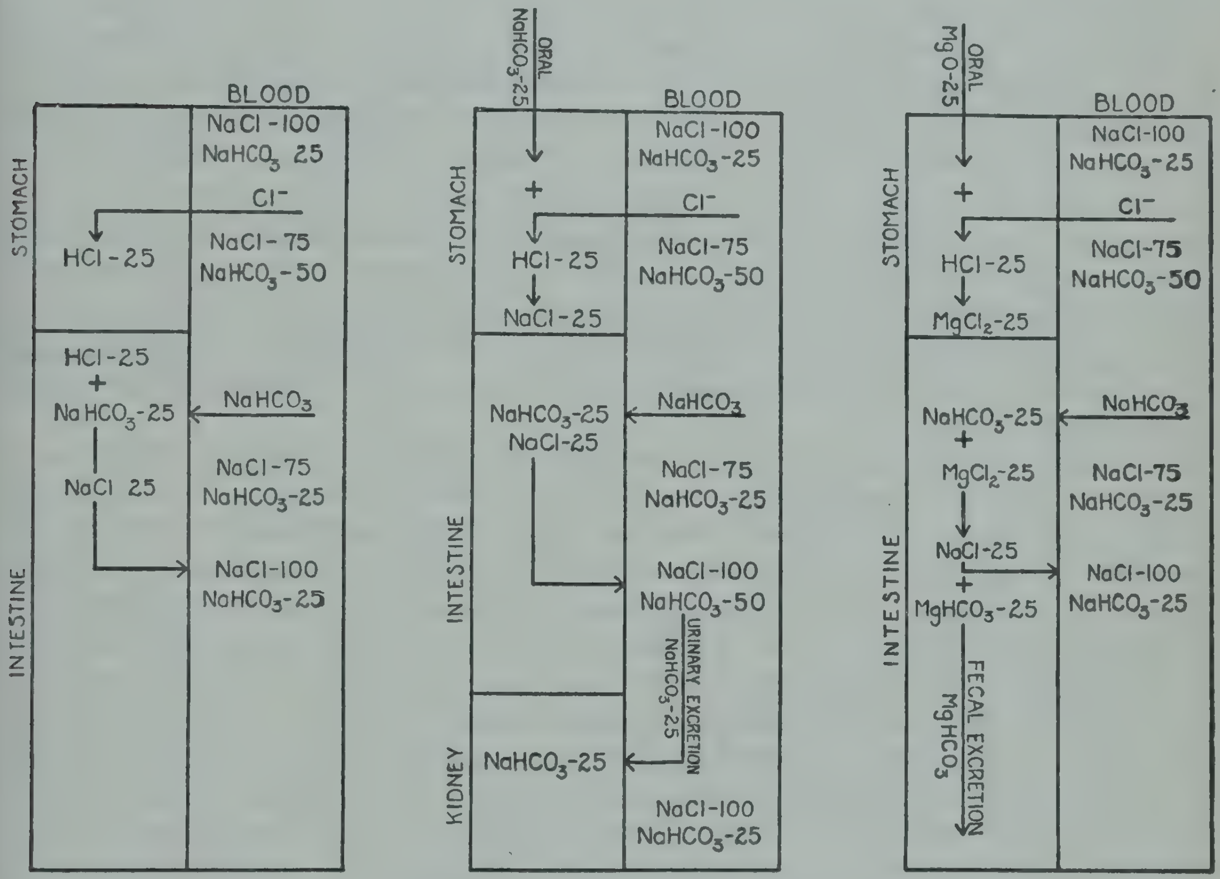

BLOOD
NaCl-100
NaHCO₃ 25
Cl⁻
STOMACH
HCl-25
NaCl-75
NaHCO₃-50
HCl-25
+
NaHCO₃-25
NaHCO₃
NaCl 25
NaCl-75
NaHCO₃-25
INTESTINE
NaCl-100
NaHCO₃-25
ORAL
NaHCO₃-25
BLOOD
NaCl-100
NaHCO₃-25
STOMACH
+
Cl⁻
HCl-25
NaCl-75
NaHCO₃-50
NaCl-25
NaHCO₃-25
NaCl-25
NaHCO₃
NaCl-75
NaHCO₃-25
INTESTINE
NaCl-100
NaHCO₃-50
URINARY EXCRETION
NaHCO₃-25
KIDNEY
NaHCO₃-25
NaCl-100
NaHCO₃-25
ORAL
MgO-25
BLOOD
NaCl-100
NaHCO₃-25
STOMACH
+
Cl⁻
HCl-25
NaCl-75
NaHCO₃-50
MgCl₂-25
NaHCO₃-25
+
MgCl₂-25
NaHCO₃
NaCl-75
NaHCO₃-25
INTESTINE
NaCl-25
+
MgHCO₃-25
NaCl-100
NaHCO₃-25
FECAL EXCRETION
MgHCO₃

FIGURE 84. *Schematic representation of the chemical changes occurring in the blood and intestinal tract incident to the secretion of digestive juices, and the effects of oral ingestion of systemic and non-systemic antacids.*

Figures in the blood columns represent concentrations in terms of mEq. per liter. Figures in the intestinal columns represent absolute amounts in mEq. obtained from one liter of blood. *Left:* The normal cycle. *Center:* The effect of a systemic antacid. Note the transient alkalosis which is corrected by the renal excretion of the excess alkali. *Right:* The effect of a non-systemic antacid. Note that the chemical changes in the blood are exactly the same as those occurring normally, despite the fact that acid has been neutralized in the stomach.

84). This delicately adjusted mechanism must function normally in order that health be maintained, and a diversion of gastric or intestinal secretions from the body is soon incompatible with life unless adequate replacement of electrolyte and fluid is made and normal renal function exists (Chapter 32).

Effects of a Systemic Antacid. Serious maladjustment of the acid-base balance can also occur, however, simply by introducing substances into the gastrointestinal tract which are potentially acid or basic. If a systemic antacid such as sodium bicarbonate is taken by mouth, the sequence of events depicted is disturbed. The hydrochloric acid of the gastric contents is neutralized in the stomach with the production of sodium chloride and carbon dioxide. Any excess of sodium bicarbonate above that required to neutralize the acid remains unchanged. The gastric contents soon pass into the duodenum, but require no further neutralization. The bicarbonate salts of the intestinal juices remain unchanged and are reabsorbed in their basic form with the sodium chloride and any excess sodium bicarbonate not neutralized in the stomach. Up to the period of reabsorption, the changes occurring in the blood are identical with those previously described, that is, the secretion of hydrochloric acid raises the concentration of the bicarbonate of the blood, but this is reduced in turn by the secretory activity of the liver and pancreas. As a result, the absorption of the intestinal contents containing unneutralized bicarbonate causes an increase in the sodium bicarbonate concentration of the blood and a rise in the pH (Figure 84). The kidney must then excrete the excess of bicarbonate in order to restore the normal chemistry of the body fluids and thus the urine becomes alkaline. Failure of the renal mechanisms to function adequately would result in alkalosis. It is unsettled as to whether the alkaline urine favors the formation of renal calculi (*see* Kretschmer and Brown, 1939; Eisele, 1940).

A point to be emphasized is that even though a systemic antacid does no more than neutralize the gastric contents and is not present in excess, indirectly it causes a rise in the bicarbonate concentration of the blood. In other words, despite the fact that the ingested sodium bicarbonate leaves the stomach as sodium chloride, nevertheless in the last analysis it is absorbed as bicarbonate, for it has prevented the neutralization by the acid gastric juice of the alkaline salts of the intestinal juices, which normally would have been reabsorbed as neutral chloride.

Effects of Non-systemic Antacids. Non-systemic antacids also neutralize the gastric contents, but do not tend to cause systemic alkalosis. Magnesium oxide may be considered an example of a non-systemic antacid. In the stomach, magnesium oxide reacts with hydrochloric acid to form the neutral salt, magnesium chloride. When the gastric contents reach the intestine, magnesium chloride reacts with sodium bicarbonate in the following manner:

$$MgCl_2 + 2NaHCO_3 \rightarrow MgCO_3 + 2NaCl + CO_2 + H_2O$$

Not only is magnesium carbonate relatively insoluble, but also the magnesium ion is absorbed from the intestinal tract at a slow rate. Therefore most of the magnesium is excreted by the bowel. Sufficient magnesium salt is in solution, however, to cause mild catharsis. The sodium chloride formed in the reaction is reabsorbed and thus, in so far as the secretion and reabsorption of ions is concerned, the events are in every way similar to those which normally occur (Figure 84). However, the gastric contents are neutralized while they are still in the stomach. In general it may be stated that the basic salts of any cation which undergoes limited absorption in the intestinal tract act as non-systemic antacids.

Effects of Adsorbent Antacids. The adsorbent antacids resemble the non-systemic antacids in that they do not cause alkalosis. In this case the reaction in the stomach is a physical one, the hydrochloric acid being adsorbed by the antacid drug. In the alkaline intestinal tract, the bound acid is freed and neutralized, and the sodium chloride is reabsorbed.

Alkalosis. Alkalosis is a condition which arises from the accumulation in the body of excessive alkali and can be induced either by the ingestion of potentially alkaline salts or by the loss of acid. In either case there is a rise in the bicarbonate content of the blood. It should be pointed out that excessive alkali in the foregoing definition refers to base in combination with bicarbonate, the so-called "available alkali" or "alkali reserve." Alkalosis can and often does exist when the concentration of total base in the extracellular fluid is diminished but at the same time the amount of base in combination with bicarbonate is increased above normal. Under such a circumstance, the blood chlorides are lowered. As has been pointed out, the pH of the blood is largely determined by the relative concentrations of bicarbonate and carbonic acid in the circulation. If, attending an increase in the concentration of bicarbonate in the blood, there is also an increase in the concentration of carbonic acid so that the pH of the blood remains unchanged, the condition is known as *compensated alkalosis.* In *uncompensated alkalosis,* the rise in bicarbonate is unaccompanied by an increase in carbonic acid and the blood becomes more alkaline.

For the most part, the end-products of metabolism are acid in reaction and the mechanisms for conservation of fixed base must be continually operative in order to maintain the electrolyte composition of the body fluids. Among the many mechanisms possessed by the mammalian organism for the conservation of base may be cited the production of ammonia by the kidney from an almost limitless supply of urea, the conversion of basic phosphate salts to acid salts by the kidney, etc. To combat alkalosis, the kidney excretes alkaline salts, and the normally acid urine becomes basic.

So preponderant are the potentially acid constituents of the diet that certain metabolic disturbances or impairment of renal function are very likely to result in acidosis. As a result of the high incidence of acidosis, medical teaching has been focused on this syndrome and it is usually readily diagnosed. Alkalosis occurs more rarely, and has received relatively little attention. Obviously, in a patient receiving systemic antacids by mouth, the failure of the kidney adequately to excrete the abnormal amount of alkali absorbed leads to alkali retention and the symptoms of alkalosis. Nevertheless, despite the wide and long-established use of antacids in therapy, the condition of alkalosis resulting from the oral ingestion of alkaline salts was not adequately described until the report of Hardt and Rivers in 1923. Subsequently the condition has been reported many times (Cooke, 1932; Jeghers and Lerner, 1936; Adams, 1939). Estimates of the incidence of alkalosis in patients receiving antacid therapy vary widely. Some clinicians claim never to have seen it, whereas others are of the opinion that a mild degree of alkalosis can be detected in a large percentage of patients, the figures ranging from eight to over 40 per cent. It is probable that the number of cases of alkalosis from antacid therapy reported in the literature represents only a small proportion of those which actually occur and that many deaths from alkalosis have been unrecognized and attributed to other causes.

Signs and Symptoms. The signs and symptoms of alkalosis may appear from a few days to weeks after the initiation of alkali therapy. They are first manifest in mild gastric complaints and distaste for food, especially milk. Nausea, vomiting and abdominal pain may follow. Mentally the patient is introspective, irritable and nervous. As alkalosis becomes more advanced, severe headache, frequently in the occipital region, dizziness and light-headedness are experienced. Neuromuscular disturbances, possibly induced by a reduction in the concentration of ionized calcium, are evidenced by aching and cramps in the muscles and joints, tingling sensations accompanied by fibrillary twitchings of the muscles, muscle spasms often first elicited by the application of the blood pressure cuff, and possibly spontaneous tetany. Others attending symptoms are a low fever, tachycardia, slow respiration, flushed face, hyperesthesia and hyperactive reflexes. If alkalosis is not corrected, eventually the patient becomes weak and prostrate, passes into a coma and dies.

Chemical Changes. Alkalosis can be positively diagnosed on the basis of the chemical changes which occur in the blood and urine. Invariably the carbon dioxide combining power of the blood is elevated, sometimes being as great as 80 to 100 volumes per cent. Associated with the increase in bicarbonate there is a decrease in the concentration of serum chloride, and this may fall to 80 mEq or less. Renal function is impaired as evidenced by the increase in the non-protein nitrogen content of the blood. This can also be demonstrated by renal function tests. The urine is alkaline, free of ammonia and chloride, and often contains albumin and casts. The chemical findings in the blood during alkalosis due to excessive antacid therapy and the changes attending proper treatment are presented in Figure 85.

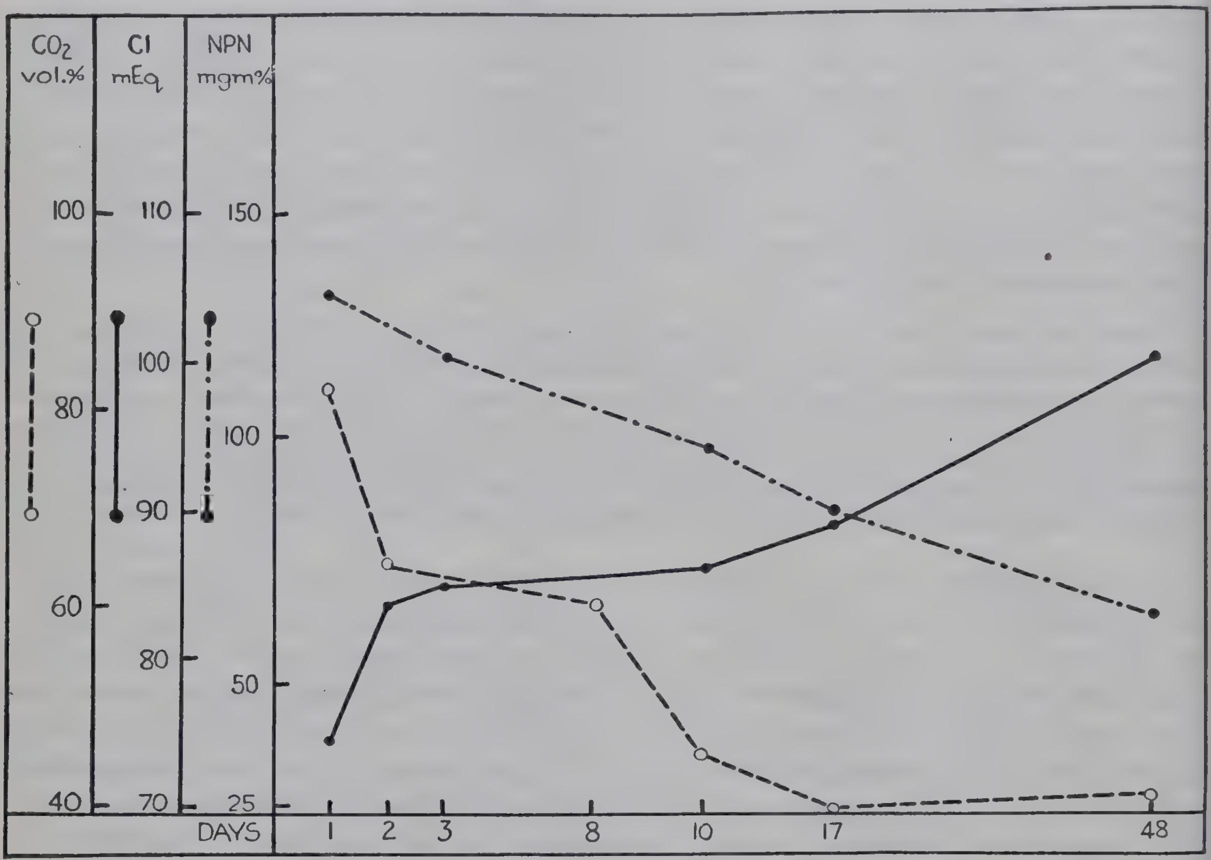


Figure 85. *Alkalosis from the use of systemic gastric antacids.*

Male, aged 31, duodenal ulcer for 13 years; self-medication with alkaline powders. Symptoms of vomiting, dizziness, nervousness, irritability and aches and pains in the legs were noted for two weeks prior to hospital admission. Physical examination was negative except for epigastric tenderness and lively reflexes. The significant changes in the blood chemistry in response to therapy are shown. Treatment consisted of daily intravenous injection of 30 grams of sodium chloride in isotonic solution for the first week and the subsequent oral ingestion of 15 grams three times daily. Muscle pains, nervousness and vomiting disappeared rapidly. (After Jeghers and Lerner, 1936. Courtesy of the *New England Journal of Medicine.*)

Treatment. The treatment of alkalosis centers around restoring the normal electrolyte pattern of the blood, all symptoms responding to this type of therapy. Obviously a condition characterized by a high bicarbonate and a low chloride content of the blood is simply and effectively combated by the administration of sodium chloride. Alkali therapy should be immediately stopped and large quantities (as much as can be tolerated without overburdening the circulation) of sodium chloride should be given intravenously in a 0.9 per cent solution. The kidney, relieved of the burden of excreting excessive amounts of alkali, and with a large available supply of electrolyte, soon functions to correct the distortion in the chemistry of the body fluid. If alkalosis is severe and it is desired to relieve the condition as rapidly as possible, an acid-forming salt such as ammonium chloride or calcium chloride may be given in a daily dose of 10 grams.

Sodium Bicarbonate (Baking Soda)

Local Actions. Sodium bicarbonate is widely used as a gastric antacid despite the fact that its many disadvantages probably outweigh its merits. Sodium bicarbonate is readily soluble and absorbable, and is the outstanding example of a systemic antacid. Because of its solubility, sodium bicarbonate has an immediate onset of action in the stomach and thus offers rapid relief from symptoms associated with the presence of hydrochloric acid. By the same token, the duration of action of sodium bicarbonate is short and the drug rapidly leaves the stomach and is reabsorbed in the intestinal tract. If the amount of sodium bicarbonate ingested is in excess of that required to neutralize the acid in the stomach at the time of administration, much of it will pass into the intestine and contribute to a systemic alkalosis without having served its function as a gastric antacid.

The reaction between sodium bicarbonate and hydrochloric acid results in the liberation of carbon dioxide. The action of carbon dioxide in the stomach has been variously described as "carminative," "soothing," and "mildly anesthetic," terms which are scarcely compatible with the phenomenon of gastric distention which it produces. In all probability the distention of the stomach may constitute a real danger in the event that an ulcer is near perforation, and the only soothing effect of carbon dioxide is that which attends the relief occasioned by the eructation of the gas.

The neutralization of the gastric contents is not without side-actions. The proteolytic enzyme of the gastric juice, pepsin, is inhibited in neutral and alkaline media and thus the gastric phase of digestion is retarded. The hydrolysis of protein, however, can proceed in the intestinal tract. Another untoward side-action is the so-called "rebound" of acid secretion which follows the alkalinization of the gastric contents. There is clinical evidence to indicate that following the neutralization of the gastric contents, the subsequent rate of secretion of hydrochloric acid is greater than if alkali had not been given. This raises the possibility of the establishment of a vicious circle by the use of gastric antacids. It must be stated, however, that experimental evidence fails to corroborate clinical observation, and the concept of the acid rebound cannot be accepted as established. An explanation which has been offered for the increased gastric secretion is the teleological one that the acid-secreting glands increase their activity in order to compensate for the alkalinization of the gastric contents.

Systemic Actions. Aside from the production of alkalosis, the systemic actions of sodium bicarbonate are relatively unimportant. There is evidence that administration of bicarbonate has an effect on carbohydrate metabolism in that the level of blood sugar may be somewhat reduced; but the mechanism of this action has not been determined, and the effect is of no practical value or significance.

Preparations. *Sodium Bicarbonate* (Baking Soda), U.S.P., B.P., is a white, crystalline, water-soluble powder. Solutions have a saline taste, and are converted by boiling to sodium carbonate. Most nostrums for the relief of untoward gastric symptoms are no more than flavored preparations of sodium bicarbonate. One gram of sodium bicarbonate neutralizes 120 cc of 0.1 N hydrochloric acid.

Therapeutic Uses. The use of sodium bicarbonate in combating systemic acidosis is discussed elsewhere (page 592). As a gastric antacid, sodium bicarbonate is chiefly employed in the treatment of hyperchlorhydria, particularly when associated with peptic ulcer. The drug is of great value when it is desired to render the urine alkaline. For example, it is employed in combination with salicylates or cinchopen in the treatment of gout in order to alkalinize the urine and thus prevent the deposition of urates in the urinary tract. It is also used in alternation with acid-forming salts to cause successive changes in the pH of the urine in order to combat infections of the urinary tract. Sodium bicarbonate is used locally on the skin for various disorders, particularly as an antipruritic, either in the form of a moist paste or a solution. The alkali is an ingredient of many solutions employed as douches, mouth washes, enemata, etc. Other uses may be found in the index.

Potassium Bicarbonate

Potassium bicarbonate has the same local actions as sodium bicarbonate and is occasionally used as a gastric antacid. It is unsuitable to combat systemic acidosis because the potassium ion is toxic and cannot replace sodium as the cation of the extracellular fluid. *Potassium Bicarbonate,* U.S.P., B.P., is a colorless, crystalline compound, more soluble in water than is sodium bicarbonate. Solutions are saline and slightly alkaline in taste and are likely to cause irritation in the stomach. Potassium bicarbonate is three times as expensive as sodium bicarbonate and offers no advantages to recommend its use.

Sodium Carbonate

Sodium carbonate is more basic than sodium bicarbonate, but is little used in therapeutics because it is extremely irritating to tissues. The official preparation is *Monohydrated Sodium Carbonate,* U.S.P. (*Exsiccated Sodium Carbonate,* B.P.), which occurs as a white, crystalline powder readily soluble in water. The preparation of sterile sodium bicarbonate solution for parenteral administration by the reaction between sodium carbonate and hydrochloric acid is referred to on page 584.

Magnesium Oxide

Magnesium oxide is one of the most widely used of the non-systemic antacids. The chemical reactions which accompany its administration have been discussed. Magnesium oxide possesses several desirable features as an antacid. The compound is insoluble and solution is not effected until the oxide reacts with hydrochloric acid to form magnesium chloride. Because of this, magnesium oxide does not neutralize the gastric contents as rapidly as sodium bicarbonate, but, on the other hand, it has a much longer duration of action. That portion of the magnesium oxide which does not react with the hydrochloric acid present in the stomach at the time of administration tends to remain in the stomach and react with acid subsequently secreted. Furthermore, there is no carbon dioxide gas formed in the reaction.

A possible disadvantage of the continued use of magnesium oxide as an antacid is the fact that the compound also acts as a cathartic and is likely to cause diarrhea. In clinical practice, this undesirable property can be circumvented by alternating the administration of magnesium salts with the basic salts of calcium, the latter compounds having a constipating effect. Also it must be kept in mind that retention of any absorbed magnesium may lead to symptoms of toxic central depression. Ordinarily the small amount of magnesium which is absorbed is rapidly excreted by the kidney, but a marked impairment of renal function can lead to a dangerous degree of retention.

Preparations. There are two official preparations of magnesium oxide, *Magnesium Oxide* (Light Magnesia), U.S.P., B.P., and *Heavy Magnesium Oxide* (Heavy Magnesia), U.S.P., B.P. The compounds are identical in chemical composition but differ in physical properties, the former being lighter and approximately five times as bulky as the latter. The increased bulk allows for a greater dispersion and a larger reactive surface, but increases the difficulty of administration. Both are white, insoluble, odorless, and tasteless powders. One gram of magnesium oxide will neutralize approximately 500 cc of 0.1 N hydrochloric acid.

Magnesium Carbonate

The antacid properties of magnesium carbonate are almost identical with those of magnesium oxide, the major difference being that the carbonate liberates carbon dioxide in its reaction with hydrochloric acid. *Magnesium Carbonate,* U.S.P., occurs as a bulky, white, hydrated powder containing approximately 40 per cent magnesium oxide. One gram, therefore, can neutralize approximately 200 cc of 0.1 N hydrochloric acid. The B.P. includes a light and heavy magnesium carbonate.

Magnesium Hydroxide

This compound also possesses the characteristic antacid properties of the basic magnesium salts. The official preparation is *Magnesia Magma* (*Milk of Magnesia*), U.S.P., an aqueous suspension of magnesium hydroxide containing not less than 7.0 and not more than 8.5 per cent of the drug. A volatile oil may be added for flavoring. Ten cc of magnesia magma are capable of neutralizing approximately 270 cc of 0.1 N hydrochloric acid. A similar preparation is *Mixture of Magnesium Hydroxide,* B.P.

Magnesium Trisilicate

Magnesium trisilicate is the newest of the group of gastric antacids, having been introduced into medicine by Mutch in 1936. From theoretical considerations and on the basis of clinical experience it promises to be a drug of significant therapeutic importance.

There are many silicates of magnesium, but the one employed as an antacid is the magnesium salt of mesotrisilicic acid ($2MgO \cdot 3SiO_2 \cdot nH_2O$). The compound is a completely insoluble, tasteless, white powder. In the gastro-intestinal tract it functions as a non-systemic antacid and an effective adsorbent. In the stomach magnesium trisilicate becomes gelatinous in consistency and reacts with the gastric contents in the following manner:

$$2MgO \cdot 3SiO_2 \cdot nH_2O + 4HCl \rightarrow 2MgCl_2 + 3SiO_2 + (n + 2)H_2O$$

The magnesium chloride reacts with the intestinal contents to form magnesium carbonate which is excreted in the feces, and sodium chloride which is reabsorbed.

The hydrated silicon dioxide which is formed in the stomach passes into the intestinal tract where it functions as an effective adsorbent.

Magnesium trisilicate possesses several unique properties. It is one of the most effective of adsorbents and thus has a greater field of usefulness than a simple chemical antacid. The consistency of the drug in the stomach is such as to allow a local adherent coating of the crater of an ulcer and thus the antacid action is localized at the desired site. The neutralizing action of the drug is prolonged, and although the greatest effectiveness is obtained during the first hour after ingestion, the drug continues to have neutralizing power for many hours thereafter. One gram of magnesium trisilicate is capable of neutralizing approximately 155 cc of 0.1 N HCl within four hours. The drug is said to be completely innocuous when taken by mouth and in therapeutic doses does not affect the motility of the gastro-intestinal tract. Large doses, however, may cause diarrhea due to the formation of magnesium chloride. Its insolubility prevents the gastric contents from reaching a higher pH than neutrality.

Preparations. *Magnesium Trisilicate,* N.N.R., occurs as a fine, white, odorless, tasteless powder, insoluble in water and partially soluble in acids. It is conveniently administered in tablet form or as a suspension of the powder. The single dose is one to four grams.

Clinical Status. Magnesium trisilicate compares favorably with other non-systemic antacids and appears to be devoid of toxic effects. Although the onset of action of magnesium trisilicate is less rapid than that of other antacids, the duration of action is significantly prolonged. Clinical reports on the effectiveness of the drug in the control of gastric hyperacidity have been uniformly favorable (Reid, 1939; Kraemer and Aaron, 1940).

Calcium Carbonate

The basic salts of calcium, like those of magnesium, are effective non-systemic antacids. Calcium chloride is formed in the stomach and this in turn reacts with sodium bicarbonate in the intestinal tract to yield sodium chloride and calcium carbonate. The sodium chloride is reabsorbed but the calcium resists absorption and is excreted in the feces. Calcium salts have a greater tendency to precipitate in the intestinal tract than do those of magnesium. Consequently they possess no cathartic action but rather tend to constipate and may form calcium concretions. It is for this reason that the basic salts of magnesium and calcium are often alternated in antacid therapy. It is claimed that calcium carbonate may act as a demulcent and also that the salt does not cause a rebound secretion of HCl. The official preparations of calcium carbonate are *Precipitated Calcium Carbonate,* U.S.P., B.P., and *Prepared Chalk,* U.S.P. The former is a more highly purified compound. Both are fine, white, microcrystalline powders. One gram of calcium carbonate will neutralize approximately 210 cc of 0.1 N HCl.

Calcium Hydroxide

The antacid properties of calcium hydroxide differ from those of the carbonate only in that there is no liberation of carbon dioxide gas accompanying the neutralization of the gastric contents. The official preparations are *Calcium Hydroxide,* U.S.P., B.P., and *Solution of Calcium Hydroxide* (*Lime Water*), U.S.P. The compound occurs as a soft, white, crystalline powder. It is relatively insoluble and the official solution which is saturated contains only 0.17 per cent of calcium hydroxide. One gram of calcium hydroxide will neutralize approximately 135 cc of 0.1 N hydrochloric acid. It would require more than 600 cc of solution of calcium hydroxide to neutralize the same amount of acid. The solution, therefore, is impractical to use as a gastric antacid.

Bismuth Salts

Several basic salts of bismuth are employed in the treatment of peptic ulcer. Those most commonly prescribed are bismuth subcarbonate, bismuth subnitrate and bismuth subgallate. These salts are not gastric antacids in the chemical sense for they are incapable of neutralizing hydrochloric acid at the pH encountered in the stomach. Rather they act as protectives and demulcents and in this manner may appreciably diminish the rate of secretion of acid.

Miscellaneous Salts

The dibasic and tribasic phosphates of calcium, magnesium and sodium have been employed as gastric antacids, but their neutralizing power is inferior to the preparations already discussed and they are seldom employed. The phosphates do not tend to cause a systemic alkalosis. The salts of strong bases and weak acids as, for example, sodium acetate and sodium citrate, are also somewhat antacid due to their buffer action in the stomach. However, they are capable of causing systemic alkalosis and therefore are not desirable gastric antacids.

Sippy Powders

Sippy powders contain a mixture of gastric antacids. They were introduced by Sippy (1915) for the treatment of peptic ulcer. In their original form they consisted of powder I which contained 0.6 gram of magnesium oxide and 0.6 gram of sodium bicarbonate, and powder II which contained 0.6 gram of bismuth subcarbonate and 2.0 to 3.0 grams of sodium bicarbonate. The powders were given alternately. Sippy powders are usually modified by individual clinicians with respect to both the amount and the nature of the ingredients. The term "modified Sippy powders" has been applied to almost any mixture of gastric antacids.

Aluminum Hydroxide

Aluminum hydroxide was introduced as an antacid in the United States in 1929. Since that time it has gained increasing favor, and is now widely employed for the neutralization of the gastric contents in the treatment of hyperchlorhydria, particularly when associated with peptic ulcer. For medicinal use, aluminum hydroxide is specially prepared in the colloidal form. In this form, the compound acts rather as a physical than as a chemical agent, and the reaction which takes place in the stomach consists chiefly in the adsorption of hydrochloric acid on the solid colloid. There is some degree of chemical neutralization but this is slight. The chemical reactions of the body fluids accompanying the secretion of the digestive juices and the colloidal adsorption of acid in the stomach have been discussed. No systemic alkalosis is produced, and this is one of the major advantages of aluminum hydroxide as an antacid.

It is probable that the action of aluminum hydroxide in the gastro-intestinal tract is not limited to adsorption and neutralization. Colloidal compounds are effective demulcents and protectives, and there is evidence that a certain degree of mechanical protection may be afforded to inflamed or ulcerated areas of the gastro-intestinal tract. Also the acidity of the gastric contents may result in the formation of small amounts of soluble aluminum chloride, and aluminum salts in solution have an astringent action, an effect which presumably might result in the diminution of the total volume of gastric secretion. However, data in regard to the effect of aluminum hydroxide on the secretory volume are contradictory and there is little to support the concept that a decrease in the volume of gastric juice can be expected.

The chronic administration of an astringent might prove to be toxic, and aluminum hydroxide has been rigorously scrutinized in regard to possible toxic actions. Clinically, the drug has proved to be benign with respect to toxic side-actions and the experimental administration over long periods of time of doses many times greater than those employed in patients has failed to reveal untoward effects (Quigley and coworkers, 1939).

The adsorptive power of aluminum hydroxide is not limited to hydrochloric acid, but probably extends to toxins, gases and bacteria. Thus the compound has also been employed as a general adsorbent in intestinal toxemia, seemingly with results as favorable as can be expected from this type of therapy. The high adsorptive property of aluminum hydroxide raises the question whether the compound adsorbs essential enzymes and in this manner interferes with the digestive functions of the gastro-intestinal tract. Specific investigations on this point reveal that digestion and absorption are not affected as evidenced by the normal composition of the feces (Beazall, Schmidt and Ivy, 1938).

Preparations. Colloidal aluminum hydroxide is available under a variety of trade names. Two types of preparations are marketed, powder and liquid. Powdered aluminum hydroxide is administered either suspended in milk or as tablets. One gram of the powder is capable of buffering 35 cc of 0.1 N hydrochloric acid to pH 4.0 within two hours. Liquid preparations consist of a suspension of hydrate of aluminum hydroxide and in this form the compound is a much more effective adsorbent. Such preparations are known as aluminum hydroxide creams. Usually the content of aluminum hydroxide is not given, but rather the antacid efficacy of the preparation is expressed as the number of cc of 0.1 N HCl neutralized in a given period of time. The available proprietary preparations neutralize about 10 to 15 times their volume of 0.1 N HCl. Solutions of aluminum hydroxide have a slightly astringent but not unpleasant taste. The cost of therapy is reasonable.

Gastric Mucin

Gastric Mucin, N.N.R., is a preparation obtained by digesting the linings of hog stomach with pepsin and hydrochloric acid and precipitating the supernatant fluid with 60 per cent alcohol. The product consists either of a white to yellow powder or of brownish yellow granules, and is marketed as gastric mucin powder or gastric mucin granules. It is well known that the mucus formed by the gastric secretory cells is both demulcent and antacid and the above product retains much of the activity of naturally secreted mucus. One gram of dried mucin combines with approximately 15 cc of 0.1 N hydrochloric acid.

The value of mucin in experimentally produced ulcers has been demonstrated by Orndorff, Fauley and Ivy (1937) who showed that the survival period of and incidence of ulcer formation in dogs with gastro-jejunal anastomoses were favorably affected by treatment with mucin. Clinical reports apparently support this experimental finding.

Mucin possesses none of the disadvantages of the chemical antacids. It cannot produce systemic alkalosis, and probably has a minimal effect on gastro-intestinal functions. It is slightly objectionable from the esthetic point of view, possessing a salty taste and a characteristic odor of peptones. Its potency as an antacid seems to be somewhat limited in comparison with the agents which act chemically and also with other adsorbents, but clinical reports as to its efficacy in ulcer therapy are favorable.

The Use of Gastric Antacids in the Treatment of Peptic Ulcer

In no field of therapy are opinions so contradictory as in the treatment of peptic ulcer. Excluding the basic problem of the indications for surgical intervention, there still remains the controversial issue as to what constitutes proper medical management. Germane to the present discussion is the rôle to be played by gastric antacids in the management of peptic ulcer. Several new drugs have been introduced as gastric antacids and have received enthusiastic acclaim from some investigators. On the other hand, Brown and Dolkart (1939) reflect the viewpoint of many gastro-enterologists when they state in an evaluation of the therapy of peptic ulcer, "From the standpoint of progress in medical management, one can summarize by saying that several dozen new variations in therapy have been introduced, enabling clinicians to obtain the same unsatisfactory results of ten or twenty years ago by a greater variety of methods." The same statement could read, "enabling clinicians to obtain the same satisfactory results," depending upon how critically one views results of therapy. The fact that a high and fairly constant percentage of patients enjoy remissions from symptoms for extended periods of time on almost any type of treatment accounts for the enthusiastic reception that greets many new drugs. However, an estimation of the efficacy of drugs must be based upon observations over periods of several years in order to record the incidence of recurrences, and under such scrutiny more basic therapy than the sporadic neutralization of the gastric contents seems to be required.

The use of gastric antacids in the treatment of peptic ulcer is based upon two principles. First, it is believed that a highly acid gastric juice provides an unfavorable environment for the healing of an ulcer and favors recurrences. Secondly, the antacids definitely provide symptomatic relief. If one wishes to argue against gastric antacids, however, it can be stated that no proof exists that there is a correlation between the acidity of the gastric contents and recurrence of ulcer, that other factors besides gastric acidity are undoubtedly concerned in the etiology of the condition, and that symptomatic relief can be obtained without the use of antacid drugs. To take a middle course one might state that there are numerous factors in the medical management of patients with peptic ulcer aside from the use of antacids, but nevertheless probably the majority of patients receive some type of antacid therapy at one time or another during the course of the disease. Antacids are unquestionably of definite value in controlling severe acute symptoms.

General Treatment. The modern treatment of peptic ulcer places emphasis on diet and rest. The patient is fed a bland diet and small meals are given at frequent intervals. Milk and cream are often prescribed between meals. Rest is essential. Some gastro-enterologists routinely recommend hospitalization for several weeks. Others, provided symptoms are not too severe, allow their patients to remain ambulatory but restrict their exercise. Antispasmodics are often prescribed, usually belladonna alkaloids or their substitutes. Mild sedatives are frequently beneficial.

Treatment with Antacids. In the event that therapy with antacids is employed, there is little doubt that preference is given to certain drugs. The ideal antacid is one that does not cause systemic alkalosis, does not cause a "rebound" stimulation of the secretion of acid, interferes least with the digestive processes, does not cause diarrhea or constipation, is not irritating to the stomach, does not release carbon dioxide upon reacting with hydrochloric acid and, lastly, is efficient in neutralizing the gastric juice. Obviously sodium bicarbonate falls far short of meeting these requirements. Although the original or a modified Sippy regimen which combines dietary therapy with the extensive use of antacid drugs has many advocates, its principles of treatment would not be violated by the substitution of non-systemic antacids for sodium bicarbonate. Such is the present tendency in the use of antacids.

Aluminum hydroxide has received much attention as a gastric antacid. Its mechanisms of action have been discussed. Intensive therapy with the drug during the acute stage of peptic ulcer has apparently yielded satisfactory results. Some clinicians recommend the use of the compound by the constant drip method. In this technic, a tube is introduced through the nose into the stomach and a two per cent suspension of aluminum hydroxide is delivered through it at the rate of five to six drops per minute, continuously for 10 days. Claims made for this method of treatment are that pain is relieved within 24 hours and that the ulcer heals rapidly. Following the 10 day period of intensive therapy, the antacid is given in doses of 10 cc, at first at two and later at four hour intervals. Woldman and Polan (1939) reported favorable results with the aforementioned therapy, even in cases with massive hemorrhage. The incidence of recurrences was apparently diminished. Others report good results with aluminum hydroxide without resorting to the use of the continuous drip method.

Another gastric antacid which seemingly possesses desirable properties is *magnesium trisilicate*. The compound is conveniently administered in the form of tablets containing 0.5 gram. The tablets are chewed before swallowing. The dose is one or two grams taken midway between the particular feedings constituting the ulcer diet. The advantages of magnesium trisilicate as an antacid have been discussed in connection with its pharmacology.

Gastric mucin is another antacid which has found considerable favor in therapy. The compound is given at intervals of two hours or more in a dose of 2.5 grams. Various investigators report that gastric mucin is useful in controlling acute symptoms and some are of the opinion that the continued use of mucin significantly diminishes the incidence of recurrences.

Whether the antacids mentioned are of greater value than the older non-systemic antacids, such as the salts of magnesium and calcium, is difficult to determine. At present they are the preparations which are being actively investigated and much of the current clinical literature pertains to their use. Compounds such as aluminum hydroxide, magnesium trisilicate, and gastric mucin differ from the older antacids in that they are demulcents and adsorbents and this may represent a true advantage. Many years will be required before it is definitely known whether they represent significant advances in the medical management of peptic ulcer.

DIGESTANTS

Digestants are drugs which promote the process of digestion in the gastro-intestinal tract. They have a limited usefulness in the treatment of conditions characterized by a lack of one or more of the specific substances which function in the digestion of foodstuff in the alimentary tract. Thus they may be classified in a general way as drugs used for replacement therapy in deficiency states. The digestants commonly employed are hydrochloric acid, the enzymes of the stomach and pancreas, and bile.

Hydrochloric Acid

A deficiency in the secretion of hydrochloric acid occurs in approximately 10 to 15 per cent of the general population. The condition is known as *hypochlorhydria. Achlorhydria* may be associated with gastritis, gastric carcinoma, pernicious anemia, and numerous other conditions. On the other hand, it is frequently encountered in individuals in whom there is no demonstrable gastric lesion and who are otherwise quite normal. The incidence of idiopathic achlorhydria is greatest among elderly persons.

The physiological functions of hydrochloric acid in the gastro-intestinal tract are numerous. The mineral acid converts pepsinogen to active pepsin and supplies the acid medium essential for the proteolytic action of this enzyme. Hydrochloric acid renders the gastric contents relatively sterile. It has been claimed that acid plays a rôle in the control of the tone of the pyloric sphincter and that this is one of the mechanisms operating in the normal emptying of the stomach. Acid gastric juice in the duodenum may also further stimulate gastric secretion, and it may promote the secretory activity of the pancreas and liver. Lastly, an acid reaction in the upper portion of the intestinal tract aids in the solution and absorption of certain essential inorganic salts, among which may be mentioned the salts of calcium and iron.

Despite the number and apparent importance of the functions of hydrochloric acid, the symptoms of achlorhydria are poorly defined. Indeed, individuals who show on repeated examination complete absence of free hydrochloric acid in response to such a powerful secretogogue as histamine may experience no gastro-intestinal symptoms, and the secretory defect may be discovered only in the course of routine examination. The symptoms of other persons with achlorhydria are more definitely related to the attending disorder which gave rise to the achlorhydria. However, certain symptoms may at times be attributed to achlorhydria itself despite the fact that they do not always accompany the absence of acid in the stomach. These include vague epigastric distress and fullness after meals, belching and abdominal distention, coated tongue, nausea and possibly vomiting, and morning diarrhea (gastrogenous diarrhea). Hydrochloric acid is effective in relieving this syndrome in a significant percentage of cases.

Pharmacological Actions. High concentrations of hydrochloric acid are corrosive and preparations for oral administration must be suitably diluted. In low concentration, hydrochloric acid increases somewhat the acidity of the gastric contents. The therapeutic dose of hydrochloric acid, which is taken during and after a meal, is usually not sufficient to cause the appearance of free hydrochloric acid in the stomach. Rather, most of the acid is bound by the gastric contents.

The absorption of a large amount of hydrochloric acid leads to a rise in the chloride and a depletion in the bicarbonate content of the blood. In the excretion of the ion, in order to prevent the depletion of fixed base, the chloride is combined with ammonia in the kidney. In this manner, the acid-base balance of the blood is not affected. Clinically, hydrochloric acid is not employed when it is desired to produce acidification of the body fluids (as for the promotion of diuresis) for the reason that it is much simpler to administer potentially acid salts such as ammonium chloride and calcium chloride.

Preparations. *Diluted Hydrochloric Acid,* U.S.P., B.P., contains 10 per cent of hydrochloric acid. The preparation is much too strong to be taken by mouth and should be further diluted with 25 to 50 volumes of water. There are several proprietary drugs which supposedly release hydrochloric acid in the stomach and possess the advantage of being solids. Such preparations are usually hydrochlorides of amino acids, and the one that has been most carefully studied is the hydrochloride of glutamic acid. It has been claimed that glutamic acid hydrochloride is more effective than hydrochloric acid in causing the appearance of free acid in the stomach (Shay and Gershon-Cohen, 1936).

Therapeutic Uses. The only proved therapeutic use of hydrochloric acid is in the treatment of gastric achlorhydria. The dose of hydrochloric acid to be employed has been the subject of considerable discussion. The ordinary therapeutic dose of hydrochloric acid (1.0 to 2.0 cc) is insufficient to allow the appearance of free acid in the stomach; but, nevertheless, for some unexplained reason, it is often effective in relieving the symptoms of achlorhydria. Some clinicians, however, recommend that the drug be given to the limit of tolerance and claim that optimal results can be obtained only with doses sufficiently large to cause free acid to appear in the stomach. For this purpose, they administer 10 cc of diluted hydrochloric acid further diluted with water, during and after each meal, usually two cc at 15 minute intervals. Ten cc of 10 per cent hydrochloric acid is the equivalent of approximately 300 cc of 0.1 N hydrochloric acid, and a dose of this magnitude approaches the amount of acid which normally would be secreted by the stomach in response to a single meal. If large amounts of hydrochloric acid are prescribed, the administration of potentially alkaline salts in the form of fruit juices or sodium citrate is advisable in order to prevent any possibility of an uncompensated acidosis.

When drinking hydrochloric acid solutions, the teeth should be protected by the use of a glass tube, otherwise the acid solution may have a solvent action on the dental enamel. The subsequent use of a neutralizing alkaline mouthwash is also recommended.

Pepsin

Pepsin is the proteolytic enzyme secreted by the stomach. Its physiological function in the initial hydrolysis of protein is well known. Although normally pepsin plays an important rôle in the digestion of dietary protein, its action is not indispensable. The proteolytic enzymes of the intestinal tract are in themselves capable of acting on native proteins and splitting them to amino acids. Consequently no serious digestive disturbance can be attributed to the absence of pepsin.

A complete deficiency in the secretion of pepsin does not occur except as an accompaniment of achlorhydria. In no instance is an acid gastric juice devoid of enzymes. However, achlorhydria is not necessarily accompanied by an absence of pepsin. The condition in which the stomach fails to secrete both acid and pepsin in response to an adequate stimulus is known as *gastric achylia.* Gastric achylia is most frequently observed in individuals suffering from pernicious anemia or gastric carcinoma.

The symptoms of gastric achylia cannot be directly attributed to the lack of pepsin. Seemingly, the deficiency of hydrochloric acid is of greater consequence. Therefore, in the treatment of achylia, hydrochloric acid is often used alone, although pepsin is sometimes simultaneously prescribed.

Preparations. *Pepsin,* U.S.P., B.P., contains a proteolytic enzyme obtained from the glandular layer of fresh hog stomach. It is marketed in the dried form and varies in appearance from a white amorphous powder to brown scales or spongy masses. Official preparations of pepsin must be assayed to determine their proteolytic activity. The activity is adjusted by appropriate dilution with lactose of the pepsin-containing powder so that one part of the final pepsin preparation will digest 3000 times its own weight of egg albumen (B.P., 2500 times). The details of the method of assay are given in the U.S.P. Numerous other preparations of pepsin are official in the N.F.

Therapeutic Use. Pepsin is employed in the treatment of gastric achylia, but there is little evidence that it serves a useful purpose. Although it is rational to correct the deficiency of gastric achylia by the administration of both hydrochloric acid and pepsin, there are few data to indicate that the enzyme contributes to the relief of symptoms. Seemingly proteolytic digestion proceeds adequately in the absence of pepsin. Also it is believed by several investigators that the administration of hydrochloric acid alone in the majority of cases results in some secretion of pepsin by the gastric glands. If employed, the dose of pepsin is from 0.5 to 1.0 gram, taken after meals. The *Elixir of Pepsin,* N.F., may be prescribed in a dose of from 10 to 20 cc.

Pancreatic Enzymes

The enzymes of the pancreas are obtainable in a preparation known as *Pancreatin,* U.S.P., B.P. Pancreatin is an amorphous powdered substance containing enzymes, principally amylopsin, trypsin and steapsin, obtained from the fresh hog pancreas. Official U.S.P. preparations must be capable of converting 25 times their own weight of starch into soluble carbohydrates and 25 times their own weight of casein into proteoses. Similar standards exist for the B.P. product.

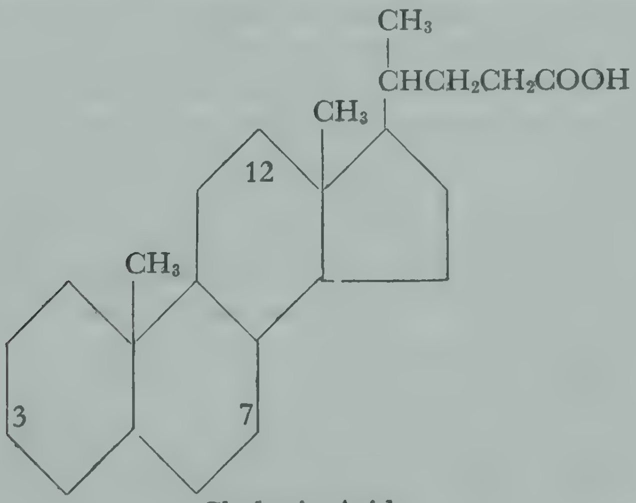
Pancreatin has been employed in ill-defined digestive disorders, but the use of the preparation is irrational. A large part of the activity of pancreatin is probably destroyed in the stomach, and even if the enzyme is prescribed in a manner designed to prevent destruction in the stomach it is doubtful whether it can significantly augment digestive processes in the small bowel. Proprietary mixtures of digestive ferments, which contain both gastric and pancreatic enzymes, are worthless. If the mixture is originally prepared from active enzymes, the latter would probably digest each other.

Bile, Bile Salts and Bile Acids

The important functions of the bile in digestion are well known. Bile is essential for the normal digestion of fats and the absorption of fatty acids. It functions in digestion by emulsifying fats and by activating pancreatic lipase. The bile salts are necessary for the normal absorption of fats and probably combine with fatty acids before absorption. The bile salts are also essential for the optimal absorption of fat-soluble substances such as carotene, vitamin A, vitamin D and vitamin K. In addition it has been claimed that bile has an antiputrefactive action in the small intestine and also that bile is mildly cathartic. The digestive functions of the bile, however, are by far the more important.

Constitution of Bile. Bile is composed chiefly of the bile salts, bile pigments, cholesterol and lecithin. Of these constituents, the bile salts are probably the most important, and account for the major physiological and pharmacological properties of the bile.

Chemistry of the Bile Salts and Bile Acids. The bile salts are combinations of the bile acids with the amino acids, taurine and glycine. The amino acids are joined to the bile acids in a peptide-like linkage. Bile salts are stable compounds, resist hydrolysis by proteolytic enzymes in the intestine and after secretion are reabsorbed as such. The bile acids are derivatives of cholanic acid which in turn is a derivative of cyclopentenophenanthrene. Thus the bile acids are chemically related to the sex hormones, the adrenal cortical hormones, and to vitamin D and cholesterol. Cholanic acid has the following structural formula:



Cholanic Acid

The most important bile acid is cholic acid which has three hydroxy groups placed in positions 3, 7 and 12. Thus cholic acid may be designated as 3, 7, 12, trioxycholanic acid. Another acid found in human bile is desoxycholic acid which has only two hydroxy groups and which can be designated as 3, 12, dioxycholanic acid. Many commercial preparations of bile acids, however, are not the naturally occurring bile acids but rather their oxidation products. The oxidation of cholic acid changes the hydroxy groups to ketone groups and results in the formation of 3, 7, 12, triketocholanic acid.

Preparations. Preparations of bile and its constituents for therapeutic use comprise several classes and include natural bile, natural bile salts (bile acids in conjugation with taurine and glycine), and triketocholanic acid. The only official preparation is *Ox Bile (Fel Bovis),* U.S.P., which is no more than the fresh bile of the ox. It is dispensed as the *Extract of Ox Bile,* U.S.P., which is a dry powder, one gram of which represents eight cc of ox bile, and the dose of which is approximately 0.5 gram. The B.P. contains a similar preparation. A concentrate of ox bile which has been freed of bile pigments and which contains approximately 50 per cent of natural bile salts is *Glycotauro,* N.N.R. It consists of a semifluid mass marketed in capsules. The natural bile salts can be isolated from bile comparatively free of all other constituents, and such preparations are also available (*Bile Salts,* N.N.R.). *Decholin,* N.N.R., and *Decholin Sodium,* N.N.R., are preparations of triketocholanic acid and its sodium salt, respectively. They are colorless. crystalline, bitter powders. The latter preparation is dispensed in ampules in 20 per cent solution for intravenous administration. *Ketochol* is another preparation of triketocholanic acid.

Pharmacological Actions. Most of the actions of bile can be attributed to the bile salts. The most important pharmacological action of bile salts from a therapeutic point of view is the ability to stimulate the flow of bile. Of all the substances which are known to stimulate the secretion of bile (choleretics), the bile salts are the most effective. In earlier studies of substances increasing the flow of bile, only the volume of bile produced was measured. However, with the advent of chemical methods for the quantitative analysis of the individual constituents of bile, the various choleretics have been investigated with respect to their stimulation of the formation of the individual biliary constituents. Germane to the present discussion is the variation in the hepatic response to the various types of bile acid and bile salt preparations. Thus Schmidt and coworkers (1938) found that whereas the natural conjugated bile salts produced a true choleresis in dogs, in that both the volume and the constituents of the bile were increased in amount, the unconjugated ketocholanic acid preparations increased the volume of the bile (hydrocholeretic action) but at the same time the total content of bile salts, pigment and cholesterol was decreased. Inasmuch as there was an *absolute* decrease in the synthesis of natural biliary constituents, Schmidt and coworkers raised the question whether the unconjugated ketocholanic acid is a hepatotoxic agent since it suppresses hepatic function. Other hepatotoxic agents such as chloroform and phosphorus have a similar depressant effect on the formation of natural bile acids. However, the administration of unconjugated ketocholanic acid preparations to experimental animals over extended periods of time failed to cause any hepatic injury (Berman and coworkers, 1940). It is of interest to note that Schmidt and his associates found that ketocholanic acid conjugated with glycine and taurine did not depress the formation of the biliary constituents and it may be that bile acids in the unconjugated form are not true choleretics.

Miscellaneous Choleretics. It has been claimed that various other substances stimulate the flow of bile. The investigations of Schmidt and coworkers (1938), however, indicate that none of these deserves such a reputation. Thus no choleretic action was observed after the administration of calomel, ammonium chloride, calcium gluconate, mucin and chondroitin, all of which have been reputed to be beneficial in conditions associated with hepatic disturbances. The salicylates were found to increase the volume of bile but to depress the formation of bile acids.

Toxic Actions of Bile. The toxic actions of bile are of interest both because bile is used as a therapeutic agent and because significantly increased concentrations of the biliary constituents can be found in the blood of patients with biliary obstruction. Although it is generally agreed that bile is highly toxic, there is controversy as to the particular constituents of bile which are responsible (*see* Horrall, 1931; Sobotka, 1937). The consensus of opinion indicates that the bile salts as such can account for most of the toxic actions. The outstanding effects of the parenteral administration of bile are on the circulatory and neuromuscular systems. Following intravenous injection of bile salts there is a marked fall in blood pressure accompanied by a bradycardia. When perfused through the isolated heart, the bile salts decrease the rate and amplitude of contraction and produce arrhythmias eventually terminating in ventricular fibrillation (Wakim and coworkers, 1939).

The circulatory response has been attributed in the past to a stimulation of the vagal nerve endings, but the more recent knowledge of the mechanism of action of drugs affecting organs innervated by the autonomic nervous system challenges the belief that chemical substances excite nerve endings. Bile salts have been shown to inactivate cholinesterase (Sobotka and Antopol, 1937) and it may be that the mechanism of the cardiac slowing is due to a decreased rate of hydrolysis of acetylcholine. In other words, the actions of bile salts may be likened to those of physostigmine. In keeping with this concept it has been observed that the parenteral administration of bile increases the motor activity of the gastro-intestinal tract. Still more pertinent are the effects of bile salts on the transmission of the nerve impulse to voluntary muscles. Small doses cause skeletal muscular hyperactivity, twitchings and spasms, and a decrease in the threshold for effective stimuli. Large doses even depress the myoneural junction (Ries and Still, 1930). Lastly, in this chain of argument, it has been shown that the cholinesterase activity of the serum in jaundiced individuals is appreciably decreased, and the possibility has been entertained that some of the symptoms of biliary obstruction, such as bradycardia and sweating, may have their origin in a decrease in the activity of cholinesterase (Sobotka and Antopol, 1937).

Miscellaneous Actions. It has been claimed that bile stimulates the musculature of the gastro-intestinal tract, and the bile salts have been classified as *cathartic* drugs. It is doubtful, however, whether the oral administration of bile salts has a significant effect on the motor activity of the gastro-intestinal tract. Greater stimulation follows their parenteral administration.

The bile salts have certain *local actions* of interest. Inasmuch as bile is widely regarded as exerting an antiputrefactive action in the intestinal tract, the effect of the biliary constituents on various bacteria has been studied. That bile is not toxic to all microörganisms is evident from the fact that the biliary tract itself is liable to infection. However, bile does exert a bacteriostatic action on some species of microörganisms and has a lytic action on pneumococci. Dilute solutions of bile acids hemolyze red and white blood corpuscles.

Therapeutic Uses. The bile salts are rather widely employed in various types of hepatic disorders without a clear conception of therapeutic objectives. The absence of bile in the intestinal tract leads to deficiencies in digestion and absorption. The question is whether to use bile preparations by mouth to correct the condition. In the event of prolonged surgical drainage of the biliary passages or in patients with biliary fistulas, in which instances the bile is deflected to the outside of the body, the administration of bile salts seems to be indicated, especially if nutrition is impaired. Orally administered preparations serve two purposes. In the intestinal tract the bile salts aid digestion and absorption, and after the bile salts are absorbed they act as choleretics and facilitate biliary drainage. In biliary obstruction, however, despite the fact that it may be desirable to have bile in the lumen of the bowel, the administration of bile as well as the consequently enhanced production of bile salts by the liver may increase the level of these substances in the blood. Nevertheless, in patients with obstructive jaundice to whom it is often desirable to administer certain of the fat-soluble vitamins, the presence of bile in the intestinal tract is essential for adequate absorption. The use of bile salts in conjunction with the oral administration of vitamin K concentrates in combating the hemorrhagic diathesis of biliary obstruction is discussed elsewhere (page 1297). Obstructive jaundice may also be associated with a deficiency of vitamin A and the accompanying symptom of nyctalopia, especially if the patient is on a low fat diet. If vitamin A preparations are prescribed, the vitamin is absorbed more readily if one to two grams of bile salts are administered at the same time.

Best and coworkers (1939) advise the use of bile salts for the purpose of removing small calculi inhibiting the flow of bile through the common bile duct. For this purpose they employ bile salts as choleretic agents to increase the pressure behind the obstruction in conjunction with antispasmodics such as nitroglycerin and atropine. In addition, they administer magnesium sulfate to relax the sphincter of Oddi. This method of treatment is contraindicated in patients with jaundice and complete obstruction of the common bile duct.

In disease of the biliary tract unassociated with acute hepatitis, a copious flow of bile of a low viscosity is desirable (Ivy and Berman, 1939). For this purpose a preparation having a hydrocholeretic action should be chosen (Greene and Farrell, 1940). The rationale for the use of choleretics is to prevent ascent of infection along the biliary passages.

The bile salts have also been recommended for their choleretic action in the treatment of functional hepatic insufficiency, hepatic jaundice, and in cirrhosis and chronic passive congestion of the liver. The true worth of the bile salts in these varied conditions is difficult to evaluate. The bile salts have also been employed for the purpose of outlining the bile ducts at operation, and to accelerate the appearance of the gall bladder shadow and hasten the elimination of residual tetraiodophenolphthalein in the roentgenological visualization of the gall bladder. When a rapid onset of action is desired at operation or for roentgenological purposes, pure preparations of the sodium salts of bile acids may be given intravenously. The dose is 0.5 to 2.0 grams. The cathartic action of bile has been greatly exaggerated and its use in obstipation is probably of little benefit.

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CHAPTER 46

CATHARTICS

Cathartics are drugs which promote defecation. There is a needlessly large number of such drugs available. The cathartics are probably used more than any other class of medicinal compounds. This is not an index of their usefulness or value but rather is an indication of the misconception which exists as to their worth.

The cathartics are so numerous as to require classification. This has been done in a variety of ways. The drugs may be classified according to the intensity of their action, and thus can be designated as laxatives, purgatives and drastics, in the order of increasing potency. The group can also be delineated according to site of action, or by the interval of time before they are effective. The most illuminating classification, however, is that which takes into account both their mechanism of action and their chemical nature.

Cathartics act by one of three fundamental mechanisms. The irritant cathartics are drugs which irritate the intestinal tract and thus increase its motor activity. This leads to a rapid propulsion of the intestinal contents and the passage of a stool which may vary in nature from one that is formed to one that is liquid, depending upon the degree of irritation. The bulk cathartics increase the contents of the intestinal tract and are thus more physiological in action. They consist either of hydrophilic colloids which resist destruction in the gastro-intestinal tract, of indigestible fiber or of inorganic salts which are slowly absorbed from the intestinal tract and thus hold water at that site due to the osmotic pressure which they exert. The emollient cathartics lubricate the intestinal tract and thus facilitate the passage of feces.

The following classification includes only the more important cathartic drugs and indicates those preparations which will be discussed.

Irritant Cathartics

- Emodin Cathartics
  - Cascara Sagrada
  - Senna
  - Rhubarb
  - Aloe
- Resinous Cathartics
  - Jalap
  - Colocynth
  - Elaterin
  - Podophyllum
- Irritant Oil Cathartics
  - Castor Oil
  - Croton Oil
- Miscellaneous Cathartics
  - Phenolphthalein
  - Mercurous Chloride

Bulk Cathartics

- Saline Cathartics
  - Magnesium Sulfate
  - Magnesium Oxide
  - Magnesium Citrate
  - Magnesium Carbonate
  - Sodium Sulfate
  - Sodium Phosphate
  - Potassium and Sodium Tartrate
- Hydrophilic Colloids and Indigestible Fiber
  - Agar
  - Psyllium Seed
  - Bran

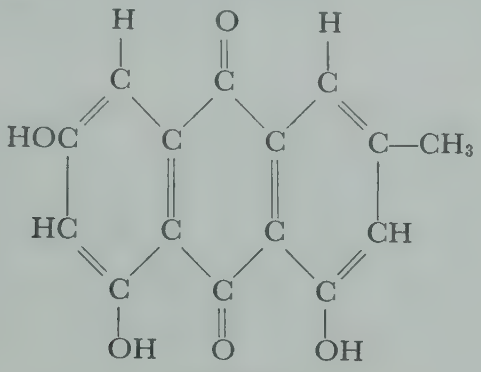
Emollient Cathartics

Liquid Petrolatum

Vegetable Oils

Emodin Cathartics

The emodin cathartics are also known as the anthracene cathartics. The principal members are *cascara sagrada, senna, rhubarb* and *aloe.* The active constituents are anthracene derivatives, of which emodin (trioxymethyl-anthraquinone) is the most important one, derivatives of it being present in all drugs in the group. Emodin has the following structural formula:



Emodin

The individual members of this group of drugs vary in their properties and activity because of the presence of constituents other than anthracene in the crude preparations which are employed, the manner in which the active principle is bound, and its ease of liberation. Consequently, although the emodin cathartics possess many actions in common, each one has individual characteristics which will be discussed.

The emodin cathartics act only on the large intestine, and the motor activity of the small bowel is uninfluenced. In the large bowel, the propulsive movements are greatly stimulated due to an irritant action, and this causes a prompt passage of the fecal contents. The time required for the drugs to traverse the small intestine and the necessity for a chemical liberation of the active principle delay the cathartic action. Consequently they are seldom effective before six hours after their administration and at times do not act before 24 hours.

The active principles of the emodin drugs are absorbed in part from the intestinal tract, and are excreted in the body fluids. During lactation, they may appear in the milk in sufficient amount to affect a nursing infant. Certain constituents of the crude drugs are excreted into and color the urine. After the administration of senna and rhubarb, chrysophanic acid is excreted by the kidneys. This compound colors an acid urine a yellowish-brown and an alkaline urine a reddish-violet. Patients should perhaps be forewarned of this fact.

In individuals who have taken the emodin cathartics, especially cascara, over extended periods of time, a melanotic pigmentation of the rectal mucosa has been observed. This may be a puzzling feature on proctoscopic examination unless the physician can elicit a history of cathartic medication (Bockus and coworkers, 1933).

Cascara Sagrada. Cascara sagrada (sacred bark) is obtained from the bark of the shrub *Rhamnus purshiana.* This bark was used as a cathartic by the Indians of California. Cascara sagrada is one of the most extensively employed cathartics. Its action is mild and unaccompanied by discomfort or griping. A therapeutic dose of this drug will cause a single evacuation of the bowel in approximately eight hours. The stool may be solid or semifluid in character. The drug is usually taken before retiring.

Preparations and Dosage. The most effective preparation of cascara sagrada is *Fluidextract of Cascara Sagrada,* U.S.P. (Liquid Extract of Cascara Sagrada, B.P.), the adult dose of which is two to four cc. It has a very bitter taste and is therefore often objectionable. A more palatable and more commonly employed preparation is *Aromatic Fluidextract of Cascara Sagrada,* U.S.P. (Elixir of Cascara Sagrada, B.P.). Its dose is twice that of the plain fluidextract. *Extract of Cascara Sagrada,* U.S.P. (Dry Extract of Cascara Sagrada, B.P.), a powdered preparation, is available in sugar-coated tablets. The dose is 0.3 gram. It is not as reliable in action as the fluidextract.

Senna. Senna is obtained from the dried leaves of *Cassia senna,* a plant used as a cathartic by the Arabians. This drug is much more active than cascara sagrada. It usually produces a single thorough bowel evacuation within six hours after its administration. It causes considerable griping which is thought to result from the action of the resins present in the leaf.

Preparations and Dosage. The commonly employed U.S.P. preparations are *Senna,* the ground dried leaf (Senna Leaf, B.P.) and *Fluidextract of Senna* (Liquid Extract of Senna, B.P.). The doses of these compounds for adults are two grams and two cc, respectively.

Rhubarb. Rhubarb is obtained from the various species of *Rheum* growing in China. The varieties cultivated for food consumption in the United States have no cathartic action. Rhubarb is unique among the emodin group of cathartics, inasmuch as its various preparations contain tannin which has an astringent action. Consequently the evacuant action of rhubarb may be followed by a period of constipation. Indeed, when small doses are given, the astringent action may predominate and thus mask any cathartic effect. A bowel movement occurs from four to eight hours after the administration of a cathartic dose. The action of rhubarb is accompanied by very little discomfort or griping.

On rare occasions, systemic reactions result from the drug, attributable to idiosyncrasy. These are characterized by nausea, headache, and occasionally skin eruptions, which may be macular, vesicular or even hemorrhagic.

Preparations and Dosage. There are many official preparations of rhubarb. *Rhubarb,* U.S.P., B.P., consists of the dried roots of the plant and is given in the adult dose of one gram. *Extract of Rhubarb,* U.S.P., is a dried concentrate, twice as active as rhubarb itself. Its dose is 0.5 gram. *Aromatic Syrup of Rhubarb,* U.S.P., is a pleasant-tasting cathartic, too weak to be very effective in adults but often prescribed for children. The dose for an infant is 4.0 cc and this is increased to 16 cc for a child five years of age. Rhubarb and soda is a popular preparation with the laity as a combined cathartic and antacid. *Compound Mixture of Rhubarb,* N.F., is essentially this combination. Its dose for adults is 4.0 cc.

Aloe. Aloe is the dried juice of the leaves of various species of *Aloe* which grow in Africa and the West Indies. The active principle is *aloin,* a glycoside which upon hydrolysis in the intestine yields an anthraquinone derivative. Both the crude drug and aloin are employed as cathartics. Aloe is the most irritating of all the emodin cathartics. Its action is accompanied by considerable griping and pelvic vascular congestion. The effects of the drug are delayed, occurring eight to

12 hours after administration. Excessive doses may cause nephritis. Aloe has an undeserved reputation as an abortifacient.

Preparations and Dosage. The two preparations usually employed are *Aloe* (*Aloes*), U.S.P., B.P., and *Aloin*, U.S.P., B.P. Their doses are 0.25 gram and 0.015 gram, respectively. In addition aloin is an ingredient of many unnecessarily complicated and irrational cathartic mixtures. One of these which is extensively employed is *Pills of Aloin, Strychnine and Belladonna*, N.F. (A.S.B. Pills). In this preparation the strychnine is supposed to enhance peristalsis and the belladonna to prevent griping. Strychnine, however, possesses no appreciable action on the intestinal musculature in therapeutic doses. Furthermore, the alkaloids in this mixture have a short duration of action and their effect will have passed long before the aloin exerts its cathartic action. The A.S.B. pills are usually marketed with a sugar-coating, and have often been the cause of strychnine poisoning in children.

Resinous Cathartics

The cathartic resins, of which the important members are jalap, colocynth, elaterin and podophyllum, are seldom employed. All are quite irritant, produce profuse watery stools and considerable colic, and are toxic when given in high dosage. The locus of their action is on the small intestine. The only drug of this group included in the U.S.P. is podophyllum.

Jalap. *Jalap*, N.F., B.P., is the dried root of the plant *Exogonium jalapa*. It is the mildest of the resinous cathartics. The therapeutic dose, 0.3 to 1.2 grams, causes a very fluid stool within three to four hours. There is comparatively little gastric or intestinal irritation. *Compound Powder of Jalap*, N.F., B.P., which is a mixture of one-third powdered jalap and two-thirds potassium bitartrate, is given in a dose of two grams. Many other seldom employed preparations of jalap are official in the N.F.

Colocynth and Elaterin. These drugs are obtained from the fruits of the *Citrullus colocynthis* and *Ecballium elaterium*, respectively. They are intensely irritating and produce copious watery evacuations within two to three hours after administration. Overdosage leads to severe prostration. The dose of *Colocynth*, N.F., B.P., is 0.125 gram; of elaterin, three to six mgm. These drugs are rarely prescribed alone but are sometimes used in cathartic mixtures.

Podophyllum. This is commonly employed as the *Resin of Podophyllum*, U.S.P., B.P. The drug is obtained from the roots of *Podophyllum peltatum*, commonly known as the Mandrake or May Apple. The drug is an old cathartic remedy of the American Indian. The resin is a powerful irritant even when applied to the skin. In the gastro-intestinal tract, its action is roughly proportional to the dosage in which it is administered. Small amounts (up to five mgm) will produce copious soft stools within 12 to 24 hours. This is unaccompanied by any marked intestinal irritation. However, if the dose is increased, the irritating properties of the resin are clearly seen, the stool becomes very watery and may be tinged with blood. The resin of podophyllum is uncertain in its action and what may be a mild dose for one individual may purge another severely. Consequently, if the drug is prescribed, a small amount should first be given and this dose increased only if necessary. In addition to the resin, the crude dried root is also obtainable but seldom used. Its official title is *Podophyllum*, U.S.P., B.P., and the dose is 0.12 to 0.6 gram.

Irritant Oil Cathartics

Castor Oil. Castor oil, which is obtained from the seeds of *Ricinus communis*, is the triglyceride of ricinoleic acid, an unsaturated hydroxy fatty acid having the formula $C_{17}H_{32}OHCOOH$. The oil itself is a bland emollient and is employed locally on the skin for its soothing properties. Castor oil is also incorporated with alcohol and extensively used as a hair tonic, in the proportions of one part of oil to ten of alcohol.

In the stomach, castor oil behaves just as other fatty substances and retards gastric emptying time. For this reason, the drug is usually taken on an empty stomach. In the intestine, the triglyceride is hydrolyzed by the fat-splitting enzymes to glycerol and ricinoleic acid. It is this last named substance which is the active agent in producing catharsis. Ricinoleic acid is a marked irritant and stimulates the motor activity of the small intestine by a local irritant action. This stimulation leads to a rapid propulsion of the contents of the small intestine. The colon is stimulated little, for in passage through the small intestine the ricinoleic acid is absorbed in a manner analogous to other fatty acids. A therapeutic dose of castor oil will produce one or two copious semifluid stools within two to six hours after administration. There is little intestinal griping accompanying this cathartic action. The fluid nature of the stool excreted in response to castor oil is not due to diffusion of fluid into the bowel, but results from the fact that the intestinal contents are propelled so rapidly that absorption of fluid is limited.

Dose and Preparations. The adult dose of castor oil is from 15 to 30 cc. Larger amounts produce no greater effect inasmuch as the hydrolysis of the oil is self-limited. The hydrolysis of a portion of the ingested oil releases sufficient ricinoleic acid to irritate the intestine and the remainder of the acid is swept out of the bowel still combined with glycerin. For this reason, castor oil is a relatively safe cathartic. The dose for children is four cc. The preparations commonly employed are *Castor Oil,* U.S.P., B.P., *Aromatic Castor Oil,* N.F., and *Emulsion of Castor Oil,* N.N.R. The last two preparations disguise somewhat the objectionable taste of the oil. The emulsion contains only 50 per cent of castor oil and hence its dose for adults is 30 cc.

Croton Oil. Croton oil, obtained from the seeds of *Croton tiglium,* is the most drastic of all cathartics. The oil itself is very irritant by virtue of its content of "croton-resin," and its local application to the skin leads to pustulation and sloughing. Croton oil was once employed as a counterirritant, diluted in a suitable inactive vehicle. The action is so powerful, however, that the oil is unsafe to use even on the surface of the body.

Irritation of the intestine is the basis for the cathartic action of croton oil. The drug is also irritating to the mucous membranes of the mouth and stomach and may produce nausea and vomiting. Croton oil causes several copious, watery bowel evacuations within one to three hours after administration. Severe pain and griping occur. The dose is 0.06 cc, and the drug can conveniently be given on a lump of sugar or a slice of bread. It is much too drastic in action, however, to be of practical clinical importance, and should be reserved for use in veterinary medicine. Death has resulted in man from the ingestion of 20 drops of croton oil. Treatment of the severe hemorrhagic gastro-enteritis resulting from overdosage of croton oil includes the administration of demulcents, morphine for pain and diarrhea, and shock therapy.

Preparations. Croton oil has been deleted from the U.S.P. but is still an official preparation in the N.F.

Miscellaneous Cathartics

Phenolphthalein. The cathartic action of phenolphthalein was discovered in 1902 by Vamossy after the Hungarian government ordered that certain adulterated wines be identified by the addition of this compound. Since that time, phenolphthalein has been widely employed as a cathartic.

Phenolphthalein is a yellowish-white powder, insoluble in water. It is odorless and tasteless and consequently one of the most pleasant cathartics to take. For this reason, and because it is efficient in action, phenolphthalein forms the basic ingredient of innumerable proprietary cathartic preparations among them being a number of nostrums dispensed in gum and candy form.

Mechanism of Action. Phenolphthalein resists solution in the stomach. In the small intestine, it is dissolved by the combined action of the bile salts and the alkaline intestinal contents. Its action has been attributed both to a direct motor stimulation of the intestine and an indirect stimulation resulting from the irritating property of the soluble salts. The extent of irritation, however, is not great. The cathartic action of phenolphthalein is not accompanied by colic or intestinal griping. The compound exerts its greatest effect on the colon, but the movements of the small intestine are also increased. It acts within four to eight hours after administration.

Absorption and Excretion. After a therapeutic dose of phenolphthalein, about 15 per cent is absorbed into the circulation and the remainder is excreted unchanged in the feces. That portion which is absorbed is largely eliminated through the kidneys, most of it in a combined form; but a small portion, especially after a large dose, may be free in the urine (Fantus and Dyniewicz, 1938). The free phenolphthalein colors the urine red if the latter is sufficiently alkaline in reaction. Likewise that portion of the drug excreted in the stool causes a red color if the feces are alkaline. This phenomenon may be observed if an individual who has ingested phenolphthalein also takes a soapsuds enema, and the color should not be mistaken for blood. Phenolphthalein has been erroneously proposed as a diagnostic agent for determining the presence of lesions of the gastro-intestinal mucosa under the false assumption that absorption from the bowel occurs only when the mucosa is ulcerated.

If phenolphthalein is injected, a large part of the drug is excreted into the bile. Thus the compound is an active cathartic even when given parenterally. Also, some of the phenolphthalein absorbed from the intestine may be excreted in the bile. This absorption and biliary excretion may lead to a prolongation of cathartic action.

Toxicity. Phenolphthalein is relatively non-toxic even after intravenous administration. Fantus and Dyniewicz (1938) were unable to poison animals with the drug. However, there are two types of untoward reactions which may accompany the clinical use of phenolphthalein. Both are rare and should be classified as idiosyncrasies. In hypersusceptible individuals, a large dose of the drug may lead to excessive purgation, colic, palpitation, labored respiration, and possibly collapse. Despite the severity of this reaction, no fatalities have been reported. The second type of reaction is a skin rash. The eruption is polychromatic and ranges in color from pink to purple. It is distributed in macular plaques varying in size from a few millimeters to several centimeters, and is accompanied by itching and burning. In severe cases, the dermatitis may proceed to the stage of vesiculation and ulceration. Even after discontinuation of the drug, the lesions may persist for months or even years and leave residual pigmentation. Should the patient take phenolphthalein again, there occurs a flare-up of the same skin areas originally involved, indicating that there is a fixed tissue reaction. Obviously, such individuals should avoid phenolphthalein.

Preparations and Dosage. Phenolphthalein is a U.S.P. and B.P. preparation. It is conveniently prescribed in tablets or gelatin capsules. The adult dose is 0.10 to 0.20 gram. The drug may be taken at bedtime and usually exerts its effect by the following morning. Phenolphthalein is combined in many proprietary cathartics in which its presence as an active constituent is frequently not designated. It is also marketed in combination with liquid petrolatum, agar, or irritant cathartics.

Mercurous Chloride (Calomel). Mercurous chloride or calomel (HgCl) was at one time the most popular of cathartics. Bethea (1934) relates how pharmacists, during their leisure moments, would prepare calomel prescriptions in large numbers in anticipation of the steady inflow of requests for the drug. Calomel was once the favorite remedy for "biliousness." This condition was thought to be associated with a disturbance in liver function. Calomel was believed to stimulate the liver and to empty the bowel at the same time, a combination of events formerly considered to be highly desirable. The subsequent elucidation of the toxic properties of this chemical and its lack of choleretic potency have resulted in a considerable decline in the popularity of the drug.

Cathartic Action. Calomel is a very insoluble salt of mercury. After oral administration it passes through the stomach unchanged; but in the intestine, in the presence of the alkaline contents and the bile, a small portion of the mercurous chloride is converted to mercuric oxide, which is dissolved to some extent. The mercuric ion is extremely irritating to the intestinal tract and it is this action which leads to increased peristalsis and defecation. Calomel produces catharsis in about 12 hours after administration and the stool is semifluid.

Choleretic Action. For a long time it was believed that calomel increased the secretion of bile. This view was entertained because the stools discharged in response to this medicament were greenish in color, due to their high content of biliverdin. It is now known that the presence of biliverdin in the stool is not due to increased secretory activity of the liver. Rather it results from the antiseptic action of mercury which prevents the normal conversion of the bile pigment in the bowel, and from the fact that the cathartic action of the ion propels the intestinal contents so rapidly that the change of biliverdin to bilurubin has not sufficient time to occur. There is no evidence, from experiments employing biliary fistulas, of an increase in formation of bile after calomel (Schmidt and coworkers, 1938).

Absorption and Excretion. The mercury which escapes solution is excreted in the feces, and this constitutes the major portion of the ingested drug. The soluble bivalent mercuric ions are absorbed. Ordinarily, the initial liberation of mercuric ions stimulates the intestinal musculature and thus most of the calomel is swept out of the bowel unchanged. If the elimination of calomel from the bowel is perchance retarded, absorption continues and appreciable amounts of mercury gain access to the circulation.

Systemic Actions. The mercury which is absorbed exerts its characteristic effects in the body. The most pronounced action, other than the toxic ones from large amounts, is a diuresis, noted especially when there is edema (page 639).

Toxicity. Calomel in itself is an innocuous substance. The toxic effects which may arise from its administration result from the absorption of bivalent mercury ions. The administration of calomel sometimes causes systemic mercury poisoning, which is described in detail elsewhere. Toxicity is not related to the amount of calomel administered, but rather, as has already been stated, to the length of time which the drug is retained in the intestinal tract. Consequently, if calomel has been given and no catharsis is obtained from the drug, it is necessary to prescribe another agent in order to rid the bowel of the potentially toxic mercury. This is usually accomplished by the administration of a saline cathartic. Indeed, when calomel was widely used, it was common practice routinely to follow its administration with a saline cathartic after ten hours.

Preparations and Dosage. Calomel is officially known as *Mild Mercurous Chloride,* U.S.P. (Mercurous Chloride, B.P.). It is a dull white, odorless and tasteless powder. The average dose for adults is 0.15 gram. The combination of calomel and a saline cathartic leads to a very complete evacuation of the bowel. However, the action of calomel is uncertain and the drug is a potential source of danger as long as it remains in the intestinal tract. Other cathartics are safer and equally efficient and the occasion rarely arises when calomel is indicated.

Saline Cathartics

The mechanism of action of all saline cathartics is identical. Therefore, in the following discussion, the saline cathartics will be considered as a group and the distinctive features of each preparation will then be described.

Mechanism of Action. There are a number of ions which are slowly absorbed from the gastro-intestinal tract. These include the cation magnesium and the anions sulfate, phosphate, tartrate and citrate. When these ions, in the form of their salts, are taken orally they are retained in the gastro-intestinal tract for a comparatively long period of time. Under such conditions the intestinal wall acts as a semipermeable membrane between the intestinal contents and the circulation. This membrane is freely permeable to water, and consequently fluid will pass between the circulation and the intestinal tract until the solution of the cathartic salt is rendered isotonic with body fluids. When large amounts of salt are taken, the volume of water retained in the digestive tract is considerable and exerts a mechanical stimulus which increases intestinal motor activity. Consequently, there is a rapid propulsion of fluid into the colon. At this site the normal absorption of fluid is similarly impeded, and the colonic contents remain liquid and are rapidly expelled. The cathartic action of these salts may thus be likened to that of an enema. The terminal bowel is distended with fluid in each instance.

Relative Efficiency of Saline Cathartics. The efficiency of a saline cathartic depends upon the rate at which it is absorbed and the osmotic pressure which it exerts in solution. There are no data available on the comparative rates of absorption of the individual saline cathartics. For all practical purposes, however, it may be assumed that there is little variation between them in this respect, for their solutions are swept through the bowel so rapidly that there is little time for absorption to take place. The osmotic pressure exerted by a given amount of each salt varies with the molecular weight of the compound and the number of ions into which it dissociates in solution. For example, the strength of a solution of sodium sulfate (Na_2SO_4) isotonic with body fluid is 1.4 per cent whereas that of magnesium sulfate ($MgSO_4$) is 1.9 per cent. Gram for gram, sodium sulfate will hold a greater amount of fluid in the intestinal tract and presumably act as a more efficient cathartic.

The statement is often made that a saline cathartic composed of two ions which resist absorption, such as magnesium sulfate, is twice as efficient as a salt in which only one of the ions cannot be absorbed, such as sodium sulfate. This is not true, because if the anion of a salt is not absorbed it follows that an equivalent amount of cation must also remain behind.

Effect on Water Distribution. Saline cathartics may be given in hypertonic, hypotonic or isotonic solutions. Theoretically, if an isotonic solution is ingested, no water exchange takes place in the intestine, but the salt solution is merely rapidly propelled the entire length of the intestinal tract. If a hypotonic solution is given, some absorption of water may take place. If time permits, water is absorbed until the contents of the intestinal tract become isotonic with body fluids. In contrast, when the cathartic salts are given in hypertonic solution, water is abstracted from the circulation and enters the intestinal canal in order to maintain osmotic equilibrium. This water is lost in the feces. Consequently, it is possible to dehydrate an individual by the repeated administration of hypertonic solutions of saline cathartics. Indeed, these compounds are often prescribed for the purpose of ridding the body of fluid rather than for evacuating the bowel. On the other hand, if the cathartic action is sought in a patient who can ill afford to lose body fluids, these preparations should be administered with sufficient water by mouth to insure that no loss of body water occurs.

Absorption. The intestinal membranes are only relatively impermeable to the saline cathartics and some absorption of these salts takes place. That portion which gains access to the circulation is excreted by the kidneys. In most instances the absorbed salts act as saline diuretics and the flow of urine is increased. If, however, the saline cathartics are given in strongly hypertonic solution, and an appreciable amount of body water is consequently lost, there may be a noticeable antidiuresis as a result of the dehydration.

In some instances, a particular ion may have a toxic systemic action upon reaching the circulation. This is true especially in the case of magnesium. This will be discussed under the individual cathartic agents.

Magnesium Sulfate. *Magnesium Sulfate* (Epsom Salt), U.S.P., B.P., is one of the most commonly employed and efficient of the saline cathartics. It consists of colorless crystals, freely soluble in water. Both the magnesium and sulfate ions resist absorption. It has been suggested that the cathartic action of magnesium sulfate may be due to an irritant action of this salt on the intestine or to an increased secretion of the intestinal juices. However, there is no reason to invoke any mechanism of action other than osmotic retention of fluid which results in mechanical stimulation of the bowel.

The magnesium ion is toxic when high concentrations accumulate in the extracellular fluid. A considerable amount of magnesium is absorbed following the oral administration of its salts, but if the kidney is functioning in a normal manner the absorbed magnesium is so rapidly excreted that no change in the blood level of this ion can be detected. However, if Epsom salt is given to an individual with impaired renal function, the accumulation of magnesium in the body fluids may be sufficient to lead to symptoms of magnesium poisoning.

The usual dose of magnesium sulfate is 15 grams. The U.S.P. and B.P. preparation ($MgSO_4 \cdot 7H_2O$) contains seven molecules of water of crystallization. A four per cent solution is isotonic with the body fluids. Therefore the therapeutic dose of 15 grams retains approximately 400 cc of fluid in the intestinal tract. If the salt is given in concentrated solution, an appreciable amount of water can be abstracted from the body. Magnesium sulfate is an intensely bitter substance. For those who object to the taste, the compound can be prescribed with lemon juice. Strong solutions are likely to be somewhat nauseating. *Effervescent Salt of Magnesium Sulfate,* N.F., contains 50 per cent magnesium sulfate combined with an effervescent mixture of sodium bicarbonate and tartaric and citric acids. Its usual dose is 16 grams.

Magnesium Oxide. This preparation of magnesium is available as the heavy or light oxide, terms which designate the sedimentation rate. Magnesium oxide is more commonly used as a gastric antacid than as a cathartic. The cathartic action depends upon the conversion of the oxide in the intestinal tract into soluble salts. The oxide is insoluble in water and very bulky. The cathartic dose is three grams and even this amount represents a large volume of drug. The compound is mild in action and does not compare in efficiency with magnesium sulfate.

Magnesia Magma (*Milk of Magnesia*), U.S.P. (Mixture of Magnesium Hydroxide, B.P.), is a 7.0 to 8.5 per cent aqueous suspension of magnesium hydroxide. It too is more commonly used as a gastric antacid than as a cathartic. The cathartic dose of 15 cc contains only a little more than one gram of magnesium hydroxide and obviously this amount cannot retain much fluid in the gastro-intestinal tract.

Magnesium Citrate. This is an expensive though pleasant saline cathartic. The official preparation, *Solution of Magnesium Citrate,* U.S.P., is a flavored solution of magnesium citrate. An excess of citric acid and sodium bicarbonate is added for the purpose of making the solution effervescent. The dose is 200 cc, although this is often exceeded.

Magnesium Carbonate. This is yet another U.S.P. and B.P. preparation of magnesium that is more commonly used as a gastric antacid than as a cathartic. The laxative dose is eight grams. Magnesium carbonate is relatively insoluble and is milder in action than the soluble magnesium salts.

Sodium Sulfate. Sodium sulfate, also known as Glauber's salt, is one of the cheapest and most effective of the saline cathartics. It is quite equal to magnesium sulfate in activity and is non-toxic after absorption. However, it is the most objectionable of all the cathartic salts so far as taste is concerned. The U.S.P. and B.P. preparations ($Na_2SO_4 \cdot 10H_2O$) contain considerable water of crystallization. The dose is 15 grams. This dose (assuming that none is absorbed) will retain approximately 500 cc of fluid in the intestinal tract because the official hydrated salt in 3.2 per cent solution is isotonic with body fluids.

Sodium Phosphate. This is one of the most pleasant tasting of the saline cathartics. It is also quite effective, but not as drastic in action as magnesium or sodium sulfate. The adult dose of the U.S.P. preparation ($Na_2HPO_4 \cdot 7H_2O$) is four to eight grams; of the B.P. preparation ($Na_2HPO_4 \cdot 12H_2O$), two to 16 grams. Still more palatable is *Effervescent Sodium Phosphate,* U.S.P., B.P. In addition to sodium phosphate this mixture contains tartaric acid and sodium bicarbonate. It is a dry powder which, upon addition of water, liberates carbon dioxide. The cathartic dose is 10 grams.

Potassium and Sodium Tartrate. This U.S.P. and B.P. preparation is also known as Rochelle salt. It consists of colorless and odorless crystals, freely soluble in water and saline to the taste. It owes its cathartic action to the fact that the tartrates are absorbed with difficulty from the gastro-intestinal tract. The toxic action of the tartrate ion is discussed elsewhere. This toxicity is not to be feared when therapeutic doses of the salt are given orally for its cathartic effect. The tartrates are not unpleasant to the taste. The dose of Rochelle salt is 10 grams. Potassium and sodium tartrate is also available in the form of *Compound Effervescing Powders,* U.S.P., B.P., known as Seidlitz powders. This mixture is conventionally dispensed in a *blue paper* containing 2.5 grams of sodium bicarbonate and 7.5 grams of Rochelle salt, and a *white paper* containing two grams of tartaric acid. The contents of the two papers are mixed in water just before the medication is taken, and effervesce with the liberation of carbon dioxide. The powders should not be taken separately.

Proprietary Saline Cathartics. There are on the market a large number of proprietary saline cathartic preparations. These range from natural mineral waters, for which extravagant claims are made, to salts which differ little from those described above. They are sold at a price which must pay for expensive advertising as well as allow a large margin of profit to the manufacturer. The tremendous sale of these preparations is evidence of the power of salesmanship over the bowel-conscious public. Needless to say, the physician can prescribe just as effective official preparations which cost only a fraction of that of the proprietary nostrums.

Colloidal and Fiber Cathartics

Constipation may often result from the ingestion of concentrated foods of low fiber content which supply insufficient bulk for the formation of feces. Under such conditions, the use of those cathartics which increase the bulk of the intestinal contents or act as emollients or lubricants to facilitate the passage of feces is often helpful. Cowgill and Anderson (1932) studied the rate of laxation in human beings ingesting a controlled diet, and concluded that a minimum of approximately 100 mgm of fiber per kg of body weight should be taken daily in order to assure proper evacuation. The bulk cathartics can augment a diet that is deficient in indigestible residue and promote defecation without subjecting the musculature of the bowel to the undesirable action of irritating drugs.

Bran. Bran is obtained in the milling of wheat. It contains almost 20 per cent indigestible cellulose and therefore is an excellent source of roughage. Crude bran is rather unpalatable, but the processed form, which is little less effective, makes a pleasant cereal. It was thought that the phytin contained in bran was one of the factors concerned in its cathartic action, but Cowgill and Anderson (1932) demonstrated that bran washed free of this ingredient is equal in laxative potency to the unwashed. They concluded that the action of bran in promoting defecation is due entirely to its fiber content. Bran has no appreciable effect on gastro-intestinal motility (Fautus and coworkers, 1940) and must be eaten in large doses in order to be effective as a cathartic. Several tablespoonfuls a day may be taken as a cereal or in the form of special bran recipes, such as cookies and muffins.

Agar. *Agar* (Agar-agar), **U.S.P., B.P.**, is a dried mucilaginous substance obtained from various species of algae. It is rich in indigestible hemicellulose. When moistened, agar swells to form a mucilaginous mass which acts as an emollient to lubricate the intestinal tract. At the same time it adds bulk and keeps the feces moist. Agar may be obtained shredded or in the form of a coarse powder. It may be eaten as a cereal, combined in certain recipes or dissolved in hot water and allowed to jell before being taken. The U.S.P dose of agar is ten grams but this may have to be increased to as much as 40 grams before the desired effect is obtained.

Psyllium Seed. *Psyllium Seed,* N.F., is obtained from various species of *Plantaginaceae.* The seeds contain a large amount of natural mucilage and swell in the bowel to form an emollient indigestible mass. The seeds can be taken mixed with fruit juices or the gelatinous mass which results from their contact with hot water can be mixed with foods. The dose is from four to 15 grams, one to three times daily.

If psyllium seeds are ground before ingestion a pigment is released which, in experimental animals at least, darkens the kidneys, and upon microscopic examination may be found deposited in small granules in the renal tubules. Although the significance of this pigmentation is not known, it is recommended that whole rather than ground seeds be employed, and ingested without mastication. Patients should be warned to take generous amounts of water with psyllium seeds, because if the seeds are taken in excessive amounts and swallowed dry, they may possibly swell in the esophagus and thereby produce obstructive symptoms. At least two such accidents have been reported from the use of other proprietary mucilaginous bulk cathartics.

Emollient Cathartics

Liquid Petrolatum. *Liquid Petrolatum,* U.S.P., (White Mineral Oil, Liquid Paraffin [B.P.]), is a mixture of liquid hydrocarbons obtained from petroleum. The oil is indigestible and unabsorbable, and in the intestinal tract it lubricates the fecal contents and prevents their excessive dehydration in the colon. There are a number of available preparations, many being sold under trade names. They vary greatly in cost but little in therapeutic effectiveness. Therefore the cheapest mineral oil of U.S.P. quality is the preparation of choice. Both light and heavy grades of liquid petrolatum are officially designated but there is no demonstrable difference in their cathartic efficacy. The dose of mineral oil is 15 to 45 cc, usually taken at night before retiring. It should not be given with meals for it may retard gastric emptying time. There is no evidence, however, that therapeutic doses adversely affect digestion or absorption. Although mineral oil is quite tasteless, many individuals object to its consistency. This objection can be lessened by taking the oil with fruit juice or as an emulsified preparation. The latter usually contains agar, but not in a sufficient amount to contribute to the cathartic effect. If large doses of the oil are taken some of it may leak through the anal sphincter. This can be prevented to a large extent by reducing the dose or dividing it into three or four portions taken at intervals during the day.

Liquid petrolatum is a valuable agent when it is particularly desired that the feces be kept soft, as for example following hemorrhoidectomies or when straining at the stool must be avoided, as in patients with hernia, aneurysm, hypertension, cerebrovascular accidents, etc. It also has a unique usefulness in forming the basic material for a salad dressing of low caloric value for use in reducing diets.

Other Oils. *Olive oil, cottonseed oil,* and other digestible oils are sometimes employed as lubricating cathartics. A sufficient amount must be given so that enough escapes hydrolysis and absorption to lubricate and soften the feces. These digestible oils will, of course, retard gastric secretion and motility and increase the caloric intake, and they should not be employed when such effects are undesirable. The usual cathartic dose is 30 cc or more.

USES AND ABUSES OF CATHARTICS

There are only a few instances in which the use of a cathartic is indicated and, contrary to popular belief, chronic constipation does not constitute one of them. The habitual use of cathartics is a most harmful practice and may provide the basis for serious gastro-intestinal disturbances.

Proprietary cathartics are widely advertised to the public, and the belief is fostered that to miss a bowel movement is of serious consequence. The layman is easily convinced of this, for from earliest times man has ever been conscious of his bowel and purges have long been considered a panacea for many ills. The occasional taking of a cathartic can hardly be considered harmful, but the continued use of such a drug is to be deplored.

Constipation occurs frequently. The cause may be trivial and one which may disappear spontaneously or which a physician could readily correct. The average person, however, does not deem it necessary to seek medical advice for an ailment which he considers himself quite capable of treating with cathartics. The cathartic habit may arise from the casual use of these intestinal irritants. This is due to the fact that many people think it necessary to have one or more bowel movements a day. After a thorough evacuation of the entire alimentary canal by catharsis, several days may be needed before a normal bowel movement can again occur. The patient thinks himself still constipated and continues the use of his favorite remedy. After a time, his bowel becomes so spastic that he comes to rely entirely on a daily dose of cathartic for a bowel movement. Spastic colitis, dyspepsia, reflex gastric complaints, and many other functional ills are traceable to the habitual use of cathartics. So fixed a part of the daily routine does the taking of a laxative become, that the patient usually fails to mention it to his physician unless specific inquiry is made. Apart from functional disorders, there is the real danger that the repeated insults to the bowel of cathartic drugs may lead to serious organic disturbances. In addition, Meulengracht (1939) warned that the abuse of laxatives may cause a deficiency of calcium resulting in osteomalacia of the spinal column. Seldom does a physician have occasion to prescribe a cathartic. Rather his problem is to treat the end-result of the cathartic habit. For example, Soper (1938) studied 177 individuals who daily employed phenolphthalein as an habitual laxative for from two to 24 months. Despite the fact that phenolphthalein is one of the milder irritant cathartics, Soper found that 152 persons in the group suffered from catarrhal colitis, three others from chronic stomatitis, and that only 22 exhibited no signs of toxicity due to the drug.

Constipation may arise from a variety of causes and these can be classified into two main groups, organic and functional. The latter type, of course, is of particular interest for this discussion. Many of the causes of functional constipation are simple to correct if recognized. Improper diet due to low roughage, emotional instability, habitual neglect of the normal impulses to defecate due to the rush of daily events, and sedentary habits are but a few causative factors. Therapy is first attempted without the use of drugs. An adequate diet, sufficient fluid intake, exercise if necessary, the establishment of a proper "habit-time" for evacuation of the bowels, sedation and psychotherapy to overcome emotional disturbances, etc., are procedures which are often successful. These measures may be supplemented by the use of agar, mineral oil, or other emollient laxatives, or by the employment of suppositories, olive or cottonseed oil retention enemas, or occasional small mild evacuant enemas. The irritant cathartics are certainly to be avoided. There seems to be a well-established relationship between thyroid activity and the tonus of the intestinal muscles, and some cases of refractory constipation can be traced to a mild thyroid deficiency. Administration of thyroid substance yields brilliant results in these patients. Tincture of belladonna may also be used for the spastic types of functional constipation.

The patient suffering from the cathartic habit may offer a difficult therapeutic problem. Not only must the cause for the constipation be found and corrected but his psychic dependence upon the drug must be broken. This can sometimes be accomplished by correcting many of his misconceptions pertaining to the bowel. The patient should be told that a daily bowel movement is not a necessity and that in many individuals an evacuation once every two or three days is not unusual. Also constipation does not lead to the absorption of any dangerous toxins. Rather, the common symptoms such as headache, malaise, nausea, etc., have definitely been shown to be due not to toxins but to reflexes arising from the lower bowel. All these symptoms can be duplicated by distending the rectum with cotton. Also, the habitual user of cathartics should be informed not to expect a bowel movement for several days after he gives up the use of drugs. Not only does a hyperirritable bowel have to recover from repeated insult, but also the colon, kept empty by the constant use of evacuants, requires several days to fill sufficiently to initiate the defecation reflexes.

Much more dangerous than the cathartic habit is the practice of taking a cathartic for the relief of abdominal pain. An inflamed appendix can be ruptured by the resulting stimulation of motor activity. It has been statistically demonstrated by many investigators that the mortality rate from acute appendicitis is increased many fold among those patients who receive purgatives once or repeatedly subsequent to the onset of symptoms as compared with those in whom no cathartic is used (Bower, 1932; Blackburn, 1935; Bethea, 1936; Kelly and Watkins, 1939).

There are a few instances which may necessitate cathartic medication. In cases of drug or food poisoning, the saline cathartics are beneficial in flushing the offending substance from the intestinal canal. Cathartics are also routinely used after anthelmintics for the dual purpose of eliminating the parasites and the toxic vermicide (page 881). The lubricant cathartics are especially useful when it is desired to prevent straining at the stool. The saline cathartics are employed in hypertonic solution for purposes of dehydration in cerebral edema, cardiac edema, etc. Finally, castor oil is sometimes used in conjunction with quinine and pituitrin to initiate labor.

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CHAPTER 47

EMETICS AND EXPECTORANTS

EMETICS

An *emetic* is a drug which produces vomiting. Vomiting may result reflexly from an irritant action on the oropharyngeal and gastro-intestinal tracts, or directly from stimulation of the medullary vomiting center. Drugs which do not have a primary emetic action may cause vomiting after toxic doses by their effects on other organs. Pilocarpine and digitalis, for example, cause emesis through their actions on the heart.

Vomiting is accomplished by relaxation of the fundus of the stomach, inhibition of the cardia, relaxation of the esophagus, spasm of the pylorus, fixation of the thorax, and sudden contraction of the diaphragm and abdominal muscles. This increases intragastric pressure and ejects vomitus up the flaccid esophagus. The stomach itself plays a purely passive rôle. Emesis is usually preceded by more or less nausea, salivation and gastric secretion of mucus. It may be accompanied, especially if prolonged, by antiperistaltic movements of the small intestine. In addition to nausea and salivation, emesis is accompanied by weakness, sweating, lacrimation, pallor, acceleration of the pulse, and a fall in blood pressure. During the act of vomiting, the blood pressure may oscillate greatly and the respirations cease, and the heart may slow markedly. Vomiting is thus a complicated coordinated act requiring the interplay of many organic, psychic, and emotional factors and can be induced or interrupted at many points.

The pharmacological studies of Eggleston and Hatcher (1915) and Weiss and Hatcher (1923) indicate the manner in which drugs may sensitize the emetic center, even to such an extent that vomiting occurs from otherwise indifferent stimuli. For example, a number of substances, including strychnine, when applied to the floor of the fourth ventricle in experimental animals, cause vomiting if noxious afferent stimuli are entering the central nervous system, as from a painful skin area. If these sensory impulses are interrupted by local anesthesia of the skin, vomiting ceases.

In studying the site of action of emetic drugs, several established technics are available. Eggleston and Hatcher (1915) discovered that most emetic alkaloids act centrally—morphine, apomorphine, nicotine, ergot, aconitine, etc. Certain other drugs including salicylates, picrotoxin and digitalis have the same central emetic mechanism. Toxic substances produced in the body conceivably can act like emetic drugs. The two basic criteria for the central site of action of an emetic agent are the occurrence of nausea and retching movements when the entire gastro-intestinal tract is removed, and the more rapid action of smaller doses of the drug given intravenously than larger doses given orally. Emetics acting centrally are thought to lower the threshold of excitability of the vomiting center rather than stimulate the center directly. This view holds that so-called "central vomiting" is reflex in nature.

Therapeutic Uses. The therapeutic uses of emetics are limited. With the advent of the wide and skillful use of the stomach tube, emetics are rapidly being relegated to a deserved obsolescence. They have been employed in cases of acute food and drug poisoning, to subdue unruly inebriates, to stop paroxysms of auricular tachycardia, to expose malingerers, etc. More effective and safer methods are available, however, to accomplish each of these purposes. The more valid use of the emetics is for the nauseant expectorant action which some of them exert in small doses.

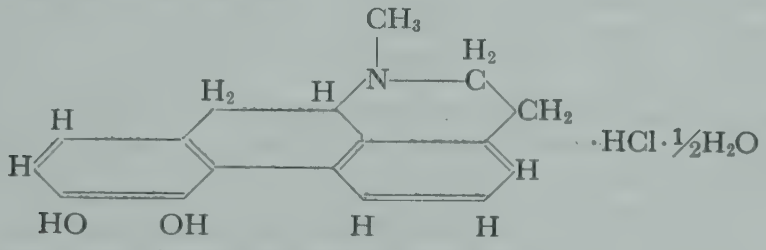
Dangers and Contraindications. Emesis induced by centrally acting drugs, especially apomorphine, may be followed by severe depression. This is particularly true if the drug is given for treatment of acute poisoning by central nervous system depressants, in which case the emesis may fail to materialize. The marked and sudden changes in blood pressure during vomiting may cause cerebral vascular accidents in hypertensive or arteriosclerotic patients. There is danger of collapse in debilitated patients, and the possibility of rupture of an aortic aneurysm, hemorrhage in pulmonary tuberculosis, and abortion in pregnancy must also be mentioned.

Classes of Emetics. Emetic drugs may be grouped according to their sites of action, as follows:

- *Central Action*
  - Apomorphine
- *Peripheral Action*
  - Mustard
  - Copper sulfate
  - Zinc sulfate
  - Tartar emetic
- *Peripheral and Central Action*
  - Ipecac
  - Emetine

Apomorphine. Apomorphine is an alkaloid obtained synthetically from morphine by changes in the molecule which produce marked differences in action. The narcotic property is suppressed and the excitant effects on the central nervous system are enhanced. Stimulation manifests itself especially on the emetic center, so that vomiting is the cardinal action of apomorphine. The use of apomorphine is practically restricted to the production of vomiting.

Chemistry and Preparations. The structural formula of apomorphine is as follows:



Apomorphine Hydrochloride

The hydrochloride is the official U.S.P. and B.P. salt available for use and consists of white or grayish white crystals which acquire a greenish tint upon exposure to light or air. It is soluble in water to the extent of one part in 50. Apomorphine hydrochloride must be rejected if its solutions develop an emerald green color as soon as the drug is shaken with 100 parts of water.

Pharmacological Action. The main action of apomorphine is to produce emesis by central stimulation of the vomiting mechanism. The drug does not cause gastric or oropharyngeal irritation, and is considerably more effective when parenterally administered than when given orally. Vomiting occurs within 10 to 15 minutes after hypodermic injection and is preceded by nausea and salivation. Apomorphine given orally is more uncertain in action, even when twice the hypodermic dose is used. Other central excitatory effects are restlessness, tremors, polypnea, and, rarely, convulsions.

Apomorphine in addition has a *central depressant* action especially if large doses are employed. Even small non-emetic doses of apomorphine may at times be hypnotic, and when a patient is already depressed full therapeutic amounts may fail to cause vomiting and may increase the intensity of the depression.

Clinical Accidents. The indiscriminate use of apomorphine as an emetic cannot be too vigorously condemned. Collapse, coma, and even death have occurred, especially if the patient is in shock from corrosive poisons, or narcotized from overdoses of sedatives. If vomiting does not result from the first dose of apomorphine, a second injection should not be given. Patients too inebriated to stand unaided are too greatly depressed to permit the safe use of apomorphine.

Dosage. The emetic dose of apomorphine hydrochloride is five to 10 mgm, the latter being a maximum dose. Although the drug is readily absorbed from all mucosal surfaces, it is given hypodermically to insure exact dosage.

Peripherally Acting Emetics. The drugs in this group produce emesis reflexly by irritation of the gastric mucosa. It has been contended that some of these agents act by means of sensory impulses carried over sympathetic afferent nerves while others act through vagal afferent impulses. Evidence for this is obtained from the use of atropine, ergotoxine and vagal section. Atropine, however, has not unequivocally been shown to paralyze the peripheral sensory components of the vagi, and vagotomy often results in spasm of the cardial portion of the stomach, thus interfering with the act of vomiting. Likewise, ergotoxine is not definitely known to act on visceral afferent endings.

Copper Sulfate. The pharmacology of copper is discussed elsewhere. As an emetic, copper sulfate is given in a dose of 0.25 to 0.5 gram in one-half glass of water (100 cc). It has been used especially in oral phosphorus poisoning, where it acts by forming an impermeable coating of precipitated metallic copper over the particles of unabsorbed phosphorus.

Vomiting occurs rather quickly after copper sulfate and before there is time for serious local irritation. Nausea is therefore brief and after-depression slight. If emesis does not occur, the copper solution must be removed by the stomach tube. As was emphasized above, the gastric tube is much safer and more effective than emetic drugs, and is certainly more available to the physician for emergency use than is copper sulfate.

Zinc Sulfate. The pharmacology of zinc is discussed elsewhere. The emetic action is the same as for copper, and the dose is one or two grams in a glass of water (200 cc).

Mustard. Mustard acts by virtue of an irritant volatile oil. The dose is a teaspoonful in a glass of warm water (not hot water). It is rather uncertain in action but certainly safer and more readily available than the metallic salts. The pharmacology of mustard is discussed elsewhere.

Antimony and Potassium Tartrate (Tartar Emetic). The pharmacology of antimony is discussed elsewhere. The emetic action is the same as for zinc and copper. Some believe that there is also a central component involved. Antimony is much more dangerous, however, than copper or zinc and is very depressing. Doses as low as 0.2 gram have proved fatal. This is due to fairly rapid absorption of antimony and its consequent systemic action. Antimony should not be employed as an emetic.

Emetics Acting Both Peripherally and Centrally. *Ipecac* and its chief alkaloid *emetine* are discussed under amebicidal agents. The vomiting caused by ipecac is both central and peripheral in origin. The drug is rarely employed to produce emesis, an action which represents an unfortunate side-effect in the use of the drug as an amebicide. Ipecac is very slow in its emetic action, requiring 30 minutes to an hour or more, and is thus not useful in emergencies. It is occasionally given as a nauseant in an attempt to cure a patient of the alcohol habit, and as a nauseant expectorant in tight or unproductive coughs. Syrup of ipecac (four to 32 cc) may be given orally to patients with paroxysmal auricular tachycardia, and once the dose is established the patient may use the drug without medical supervision. The cessation of the arrhythmia is brought about by vagal impulses arising from the act of vomiting and stimulation of the medulla. Emesis acts as a safeguard against overdosage (Weiss and Sprague, 1937). Carotid sinus pressure and other physical measures should be tried first, and mecholyl is a more effective agent (page 364).

EXPECTORANTS

An expectorant is a drug which assists in the removal of exudate or mucus from the trachea, bronchi or lungs. An expectorant may act by causing a more abundant secretion from the respiratory passages, by making the sputum more fluid and less viscous or tenacious, or by inducing coughing.

Coughing is a reflex mechanism for removal of sputum and is usually quite efficient, unless excessive so that the patient's strength is wasted, or unless dry and unproductive. Rarely are drugs used to stimulate the cough reflex, but rather the physician usually seeks to depress coughing so as to allow the patient mental and physical rest. In this manner, the act of coughing is reserved for the time when it can really be productive. A moribund or exhausted patient may be unable to cough. Aspiration by suction should then be the method of choice to clear the air passages of obstructing sputum or exudate. Atropine is also useful in such cases.

Indications for Expectorants. The use of expectorants and cough mixtures is far more of an art than a science and is bound up with the earliest practice and folklore of medicine. Years ago, many more drugs were available and used for cough and expectoration than at present, and fortunately a large number of these are now obsolete. Many patients, however, expect a "cough medicine" when they have a cough and are disappointed if one is not forthcoming.

Therapy with expectorant drugs is purely symptomatic. The indications for expectorants usually arise in inflammatory conditions of the bronchopulmonary tree, and the type of expectorant indicated varies with the stage of the disease. The type of cough, the character of the sputum and a knowledge of the underlying pathological process are the chief aids in the selection of proper therapy. For example, a cough medicine prescribed to loosen a tight cough is unnecessary and may be harmful once the stage of increased secretion is reached.

Types of Cough. Coughs may be useful or useless. The *useful cough* brings up secretion and helps drain the respiratory passages. The *useless cough* is unproductive and due mainly to mechanical irritation from pressure on the trachea or bronchi. The useful cough may take one of the following forms. The *tight* cough is one with scanty or tenacious sputum and often requires loosening. The *unproductive cough* may necessitate measures to stimulate secretion. The *loose cough* raises abundant sputum, is troublesome for this reason, and may require measures to thicken the sputum. The *insufficient* cough occurs in exhausted or moribund patients who are too feeble to raise the obstructing bronchial secretions.

Classification of Expectorants. The terms used to describe the classes of expectorants are confusing and vary with each author. The confusion has arisen largely from the words *sedative* and *stimulant.* The nomenclature and drug classification employed here are those of Brown (1937). A *sedative* expectorant refers not to sedation of the cough reflex but to the soothing of the acute inflammation by stimulation of protective secretion. A *stimulant* or *irritant* expectorant, likewise, refers not to stimulation of secretion but to stimulation of repair of a chronic inflammatory process. *Anodyne* expectorants, such as codeine, refer to those which depress the cough reflex and should not be confused with sedative expectorants.

(1) Sedative Expectorants. Drugs in this category act to lessen acute inflammation by aiding the secretion of protective mucus, and thus lessen the paroxysms of coughing and render the latter more effective. They comprise several groups of drugs, each acting in a somewhat different manner—the salines, the nauseants and the demulcents.

(2) Stimulant Expectorants. Drugs in this group act to stimulate repair in chronic inflammatory processes of the bronchial mucosa. Some are mild irritants and may act in a manner similar to that of tar in chronic skin disorders. A number of them are aromatic bodies which probably are eliminated in part by the respiratory mucous membranes. They tend to diminish secretion.

(3) Anodyne Expectorants. Drugs in this category depress the cough mechanism by a central action, and most of them belong to the opium group of alkaloids.

The expectorant drugs are classified in Table 42.

Sedative Expectorants

Ammonium Chloride. The pharmacology of ammonium salts is discussed under diuretics (page 630) and ions (page 609). The exact manner by which ammonium chloride acts as an expectorant is not understood. Some claim that the gastric irritation caused by ammonium salts causes reflex bronchial secretion; but it is difficult to see how small doses can do this, especially when little or no irritation or nausea occurs. It is not unlikely that much of the beneficial action ascribed to the salt is in reality due to the ingestion of water usually prescribed with the cough medicine.

Ammonium chloride is given for *tight* coughs in the dose of 0.3 to 0.5 gram, once every hour or two. Its action is transitory. Syrupy vehicles are best to disguise its taste, and *Syrup of Cherry* (N.F.) is frequently used. The syrups of acacia, citric acid, orange, tolu, etc., are also serviceable, and the elixir of terpin hydrate is likewise used. At least a glassful of water should be prescribed with each dose of ammonium chloride.

TABLE 42

EXPECTORANT DRUGS

SEDATIVES

SALINE	NAUSEANT	DEMULCENTS
* Ammonium chloride	Antimony and potassium tartrate	Syrup of acacia
* Ammonium carbonate	Apomorphine	Syrup of glycyrrhiza
Ammonium acetate	* Syrup of ipecac	
* Potassium citrate	Compound mixture of opium and glycyrrhiza	
* Potassium acetate		
Sodium citrate		
Syrup of hydriodic acid		
* Potassium iodide		
* Sodium iodide		
Calcium iodobehenate		

STIMULANTS

- * Creosote
- Creosote carbonate
- Calcium creosotate
- Guaiacol
- * Oil of eucalyptus
- * Oil of turpentine
- Oil of dwarf pine needles
- Turpentine
- * Terpin hydrate

ANODYNES

- Morphine
- * Codeine
- Dilaudid
- Heroine

* More commonly used expectorants.

Ammonium Carbonate. This salt acts similarly to the chloride, and is used in the same manner and dosage. It is more likely to be irritant to the stomach and in large doses produces nausea. Being an alkaline salt, it should not be given in acid syrups. Although carbonates precipitate alkaloids from their salts in watery solutions, codeine salts are exceptions and can therefore be prescribed in the same mixture with ammonium carbonate without producing an incompatibility.

Citrates and Acetates. The employment of the citrates and acetates as expectorants is mainly empirical, and it is probable that the water ingested with them is the basis for any beneficial effect. They appear to have some advantage over the acid salts, such as ammonium chloride, in patients with fever, because they are indirectly alkalinizing and thus do not favor acidosis as does ammonium chloride. They are also mildly diuretic, and may be laxative in larger dosage. The official U.S.P. and B.P. preparations are *Potassium Citrate, Sodium Citrate, Potassium Acetate* and *Solution of Ammonium Acetate. Sodium citrate* is probably the best agent to employ. Its dose is one or two grams given every one or two hours. It should be taken with at least one-half glassful of water or fruit juice. Unless diluted in this manner, it is likely to cause gastric distress. It may rarely cause urticaria. The mild salty taste is easily masked by the fruit syrups. *Potassium citrate* may be used in an identical manner.

The acetates are less palatable than the citrates, and the preferred one is *potassium acetate.* Its dose and method of administration are the same as those given above for sodium citrate. *Solution of ammonium acetate* is rarely prescribed. Its dose is 15 cc given every hour or two. It should be freshly made and is dispensed preferably in peppermint water.

Iodides. The pharmacology of the iodides is discussed elsewhere. The iodides are said to stimulate bronchial secretion and the ion is excreted by the bronchial glands. In acute inflammatory conditions of the respiratory mucosa, iodides are too irritating to be employed. They should therefore be reserved for use in the later stages of bronchitis when a tenacious sputum may be liquefied by such medication. Empirically, the iodides are widely used in many asthmatic mixtures. The iodides should not be prescribed much longer than is actually necessary to "loosen" the cough. In some patients with chronic bronchitis or asthma, iodides may be prescribed more or less continuously if they appear to afford relief. Alstead (1939), however, could demonstrate no benefit from potassium iodide either in regard to the volume or fluidity of the sputum in 17 controlled cases of chronic bronchitis. The main contraindication to the use of iodides is tuberculosis.

Most preparations of iodides are satisfactory. Sodium or potassium iodide is commonly used. The salt can be prescribed as a saturated solution and the desired amount, usually containing 0.3 gram, directed to be taken with a glassful of water or milk every two hours. When the secretory effect on the lacrimal and nasal glands becomes evident, the intervals between doses should be increased. Iodides may also be directly incorporated in more elaborate cough mixtures. For children, one part of the official *Syrup of Hydriodic Acid,* U.S.P., may be prescribed in three parts of a fruit syrup, and a dose of four cc of this mixture given every three or four hours. The adult dose is four cc of the syrup of hydriodic acid itself. *Calcium Iodobehenate,* U.S.P., may be used in doses of 0.5 gram but has no advantage over more available salts, except in patients complaining of gastric irritation from iodides. It may be prescribed in capsule form.

Antimony. This element is discussed elsewhere. As an emetic, *Antimony and Potassium Tartrate (Tartar Emetic),* U.S.P., B.P., is far too dangerous to prescribe. A much smaller dose (one to 3.0 mgm) is adequate to cause the slight nauseant action which results in loosening of a dry cough. The drug may be given in a syrupy vehicle. Tartar emetic is not employed as commonly as formerly, and may easily be discarded as an expectorant. The *Compound Mixture of Opium and Glycyrrhiza,* U.S.P., owes its expectorant action to its antimony content.

Ipecac. The pharmacology of ipecac is given under the amebicides. The *Syrup of Ipecac,* U.S.P., may be prescribed as such in the adult dose of 0.5 to 1.0 cc. For children, the dose is usually stated to be five "drops" for the first year of age, and one additional drop for each additional year. Syrup of ipecac is especially useful for croupous bronchitis in children. It may be given with saline expectorants in the same mixture. In the experiments of Alstead (1939), however, no demonstratable increase in the volume of fluidity of the sputum could be noted in 17 patients with chronic bronchitis treated with tincture of ipecac.

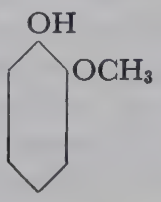
Apomorphine. This alkaloid is discussed under emetics. It is practically never used as an expectorant. Its dose for this purpose is 0.5 to 1.0 mgm, given in the form of the official hydrochloride salt.

Demulcents. Demulcent expectorants are bland substances which act by protectively coating the irritated pharyngeal mucous membrane. In this group are such vehicles as the N.F. *Syrup of Acacia* and *Syrup of Glycyrrhiza* (page 766).

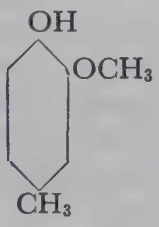
Stimulant Expectorants

Creosotes and Guaiacol. *Source. Creosote,* U.S.P., B.P., is obtained from the distillation of wood, being a mixture of phenols derived from wood tar. The type used medicinally comes especially from beechwood.

Chemistry. Creosote is a colorless or yellow inflammable liquid having a penetrating smoky odor and a burning caustic taste. The two main constituents of creosote are *guaiacol* and *creosol,* the formulas of which are as follows:



Guaiacol



Creosol

Both substances are closely related to the cresols. Guaiacol is official in the U.S.P and B.P. and constitutes about 60 to 90 per cent of creosote. It is either a colorless or yellow oily liquid, or a colorless or yellowish crystalline powder.

Absorption, Fate and Excretion. Guaiacol and creosote are absorbed from the gastro-intestinal tract and eliminated chiefly in the urine in combination with sulfuric and glycuronic acids. When therapeutic amounts of either drug are taken orally, it is claimed that none of the chemical is excreted through the lungs; but guaiacol or a derivative is found in fairly large amounts in the sputum for two to three days after it is injected as such into the blood stream.

Uses. Guaiacol and creosote at one time enjoyed a rather wide use in pulmonary tuberculosis, but this practice has fallen into deserved discard. No evidence exists to support the use of these drugs in acid-fast pulmonary infections. Fellows (1939), for example, found that the administration of calcium creosotate to patients with pulmonary tuberculosis failed to modify the volume or character of the 24-hour sputum specimens. None of the orally administered drug was excreted in the sputum, although large amounts of volatile phenols appeared in the urine, indicating intestinal absorption of the compound in man. The bacteriostatic and germicidal potency of the calcium salts of creosote and guaiacol is low (Fellows, 1937). The limited value of creosote and guaiacol compounds has been reviewed by the Council (1938), and these drugs have been omitted from N.N.R.

Guaiacol has been revived for the therapy of nontuberculous acute and chronic *lung abscesses.* There is little doubt that guaiacol or some volatile phenol derivative is excreted by the lungs provided the drug is given intravenously in the proper form and dose. Some patients are apparently improved by guaiacol therapy, the fever and cough subside, the sputum may decrease in volume and lose its foul odor, and radioscopic examination of the lungs sometimes shows early resolution of the pneumonitis and subsequent disappearance of cavitation. Unfavorable reactions do not seem to occur. The free guaiacol rather than its soluble esters should be employed. The intravenous dose is 0.3 to 0.6 gram dissolved in two cc of 95 per cent ethyl alcohol. This is diluted with 18 cc of a one per cent solution of sodium iodide. The injection is repeated every third or fourth day. The solution is stable and, if protected from light, keeps for several months before the drug precipitates out (Nammack and Tiber, 1937).

As *expectorants,* creosote compounds and guaiacol have been used empirically for the lessening of the amount of mucus in the chronic stages of bronchitis and bronchiectasis. The drugs should not be given in the acute stages because of the hyperemia they induce. Apparently they aid healing in the chronic stage of inflammation by causing irritation. The sputum often decreases in amount and is less objectionable in taste and odor. The preparations commonly used are *Calcium Creosotate,* U.S.P., 0.5 gram tablet orally, or *Creosote Carbonate,* U.S.P, 0.5 to 1.0 cc orally in milk every four hours. The former is a dark brown powder having an empyreumatic odor and a sharp characteristic phenolic taste; the latter is a clear colorless or yellowish, viscid liquid which is odorless and tasteless as a rule.

Creosote may also be employed for its stimulant expectorant action in the form of a steam inhalant in the same manner as eucalyptol, oil of turpentine, etc. Care must be taken to avoid too high a concentration of the vapor, for it is irritating to the eyes, nose, throat, and bronchi. A mild inhalant is obtained from the use of four cc of creosote in a pint of hot water. Some employ an inhalation mask (chloroform inhaler) and pour on it 0.5 to 1.0 cc of a mixture of equal parts of creosote and alcohol. Inhalations are continued fifteen to thirty minutes, more of the mixture being added as needed, and repeated at intervals. Occasionally guaiacol is used similarly to thymol as a local anesthetic in dentistry. Both guaiacol and creosote have some antiseptic and antipyretic properties but these have no clinical application.

Toxicology. Creosote and guaiacol share the same propensities for poisoning as phenol. In large doses, cardiovascular collapse is prominent. Side-effects from clinical doses are mainly those of gastro-intestinal irritation. *Guaiacol Carbonate* (N.F.) is so insoluble that it is practically non-toxic even in large doses. Much of it passes into the feces unchanged.

Terpin Hydrate. Terpin hydrate is useful as an expectorant to lessen an abundant sputum in chronic cough, especially if the sputum is quite liquid. *Terpin Hydrate,* U.S.P., is a colorless, crystalline substance with a slightly bitter taste and faint aromatic odor. It is soluble in water to the extent of one part in 200, and in alcohol, one in 13. It is prepared by the hydration of oil of turpentine and is less irritant, less toxic and more pleasant than the latter. The effective dose is 0.3 gram given orally in capsules three to five times daily. The usual dose is often too small. For example, the *Elixir of Terpin Hydrate* (N.F.) contains only 60 mgm in four cc, and therefore acts mainly as a vehicle when used in the traditional manner in cough mixtures.

Oil of Turpentine and Turpentine. A number of volatile aromatic substances are useful as stimulant expectorants in chronic inflammation of the bronchial passages. They are employed mainly as medicated vapor inhalations, and by their slightly irritative action induce hyperemia and healing. Creosote, which has been discussed, and oil of turpentine are often incorporated in inhalant mixtures. In addition, oil of turpentine is used for its local action as a counterirritant on the skin.

Source. Oil of Turpentine, U.S.P., B.P., is a volatile oil distilled from turpentine, an oleoresin obtained from *Pinus palustris* and certain other species of *Pinus.* It is a thin colorless liquid consisting mainly of pinene, $C_{10}H_{16}$, and has a characteristic odor and taste. It is soluble in oils and alcohol but not in water. *Oil of Dwarf Pine Needles,* U.S.P., contains a volatile oil similar to that of oil of turpentine. It can be used interchangeably with the latter but has a more agreeable odor.

Actions and Uses. Oil of turpentine acts as a cutaneous *counterirritant.* It may be used as a liniment undiluted or diluted in five to 10 parts of olive oil or alcohol. On subcutaneous injection, turpentine causes *sterile abscesses,* a phenomenon used in experimental studies of inflammation. As a *stupe,* oil of turpentine is often efficacious (1:250 in hot water) in relieving abdominal distention and meteorism even when other measures have failed. The skin should first be oiled with petrolatum, and the hot stupes should be replaced every five to 10 minutes until relief is obtained. The use of turpentine in enemata as an anthelmintic or amebicide is ineffective, obsolete and dangerous. Oil of turpentine may be used as an *expectorant* by putting one teaspoonful in a pint of boiling water and inhaling the steam. It is possible that the water vapor itself plays a leading part in the soothing effect on bronchial inflammation and the symptomatic relief which follows. Thus the humidity in the sick room of the patient with bronchitis should be kept above 65 per cent by various means. When the vapors of creosote, oil of turpentine, etc., are used, they should not be too strong or they may do harm, and they are not indicated in the acute stage of inflammation.

Absorption, Fate and Excretion. Turpentine is readily absorbed from the skin, intestinal tract and lungs. It is excreted largely by the kidneys. In the urine, it appears as terpenols paired with glycuronic acid. The urine has the odor characteristic of violets.

Poisoning. In small doses, turpentine causes no noticeable systemic effects. In larger doses (15 cc for children, 150 cc for adults), fatal poisoning may occur. Intoxication is characterized by pain, colic, nausea, vomiting and diarrhea; delirium, excitement, ataxia and coma; painful micturition, and albumin and red blood cells in the urine. In industry, poisoning from inhalation can occur. Treatment is purely symptomatic.

Eucalyptol (Cineol), U.S.P., B.P. This is a colorless liquid, which has a camphor-like odor and a pungent taste which leaves a cool after-sensation in the mouth. It is obtained from the volatile oil (*Oil of Eucalyptus,* U.S.P., B.P.), of the leaves of a tree, *Eucalyptus globulus.* The leaves are known as blue gum leaves. Eucalyptol also occurs in oil of cajeput. Eucalyptol is very soluble in alcohol and oils, and insoluble in water. Its empirical formula is $C_{10}H_{18}O$. Locally, eucalyptol is an irritant, and is used in medicated steam inhalations in the same manner as creosote or oil of turpentine. For this purpose, four cc may be added to a pint or quart of boiling water. It is sometimes incorporated in one to three per cent concentration in liquid petrolatum for use as a nasal spray. Oil of eucalyptus may be used interchangeably with eucalyptol. Eucalyptol imparts an odor of violets to the urine, as does turpentine. Skin eruptions may occur from small doses in patients with idiosyncrasy to the drug. Large doses (10 to 30 cc) taken internally have caused death in human beings.

Anodyne Expectorants

The anodyne expectorants consist of the phenanthrene alkaloids of opium. The actions and uses of these drugs are discussed elsewhere.

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SECTION XIII

ANTISEPTICS, DISINFECTANTS AND DRUGS USED IN THE CHEMOTHERAPY OF INFECTIOUS DISEASES

One of the most thrilling chapters in medical history is that which deals with the discovery of microorganisms and their relationship to disease. Of the many fields of study which have grown from this epochal discovery, the investigation of drugs effective against infections caused by pathogenic bacteria and protozoa has been one of the most interesting and fruitful. Almost from the beginning there have been two main lines of endeavor, the development of germicides which would be active locally, and others which would prove effective upon systemic administration. The basic problem confronting investigators was simple in principle. Effective compounds had to be found which were more toxic to microorganisms than to the host which harbored them.

With respect to the locally acting drugs, a partial solution was soon forthcoming. Within a relatively short time, an imposing number of antiseptics and germicides have accumulated. None is ideal, for each to some extent is toxic to tissue. Nevertheless, from a practical standpoint, they have largely achieved their purpose, and the degree of local injury which they cause is usually not a serious drawback. The locally acting germicides now available can be numbered in the hundreds, and new compounds are constantly being introduced. Many are unnecessary and merely contribute to the confusion which exists when numerous drugs are available for a single purpose. Others, however, represent distinct advances.

The quest for drugs to combat systemic infections was beset with greater difficulty. Here the problem of toxicity for the host could not be disregarded. Yet specific infectious diseases have yielded, one by one, to therapy with chemical agents. On a purely empirical basis, quinine had been found effective in the treatment of malaria. More noteworthy from a scientific point of view was the discovery by Ehrlich of arsphenamine and its value in the treatment of treponemiasis. Leishmaniasis yielded to compounds of antimony, trypanosomiasis to organic arsenicals, amebiasis to emetine, organic iodides and arsenicals.

The common pathogenic bacteria seemed more resistant to attack by drugs. Attempts were made to cure staphylococcal, streptococcal, pneumococcal and other bacterial infections by the systemic administration of the less toxic of the known bactericides. Claims were made that such compounds as acriflavine and mercurochrome were effective after parenteral administration in systemic bacterial infections, but these were not substantiated. Nevertheless, pharmacologists were not discouraged from testing other dyes and in 1933 it was announced that prontosil was active in combating streptococcal infections. The natural skepticism which greeted this announcement was quickly overcome when numerous reports of the truly brilliant success achieved by the drug began to appear from all parts of the world. A study of prontosil soon yielded the information that the active chemotherapeutic agent was sulfanilamide, and shortly thereafter closely related compounds including sulfapyridine were introduced. To the already long list of pathogenic microorganisms vulnerable to chemical agents were thus added the streptococcus, meningococcus, pneumococcus, gonococcus, gas bacillus and others.

One can only predict an optimistic future for the chemotherapy of infectious diseases. Many problems, however, remain to be solved. In particular, drugs must be found which are effective in the treatment of infections due to acid-fast organisms and viruses. Yet if the successes of the past thirty years are duplicated within the next thirty, Ehrlich's idealistic goal of a chemotherapeutic agent for the treatment of each infectious disease will have largely been achieved.

In the study of bactericidal drugs, a major distinction must be made between those which act locally and those which are effective after parenteral administration. Two types of organization have been employed. In those instances in which a single infectious disease is treated by a variety of chemical agents, the disease forms the nucleus for the discussion of the drugs. Thus the pharmacology of the organic arsenicals, bismuth and metallic mercury is centered around the treatment of syphilis, the pharmacology of emetine, chiniofon and vioform around the chemotherapy of amebiasis, and the pharmacology of the anthelmintics around the treatment of helminthiasis. On the other hand, when a single drug is used in the treatment of many diseases, as is the case with sulfanilamide, the drug forms the central theme of discussion.

The locally acting agents are considered together as a group. Included in this category are the genito-urinary antiseptics which, although absorbed, act at the site of excretion in essentially a local manner.

CHAPTER 48

ANTISEPTICS, GERMICIDES, FUNGICIDES AND PARASITICIDES

No group of drugs is more widely employed than the antiseptics and disinfectants. The discoveries of Pasteur, at first so difficult to impress upon the medical profession, are now embraced by the layman, often with an enthusiasm which is exceeded only by ignorance. The brilliant history of the control of sepsis is marred not so much by its failures as by the myriad of misconceptions which has been fostered in the public mind regarding the harmful nature of what often amounts to no more than a normal bacterial flora and regarding what can be done to that flora by the use of bactericidal drugs.

The problem of the indiscriminate use of bactericidal drugs by the layman was succinctly stated by McCulloch (1936) as follows, "The daily application of disinfectants to normal tissues—which is common since it has become the fashion to use medicated eye and mouth washes, sprays and douches for the nasal cavity and douches for feminine hygiene—interferes with the normal defense mechanisms of the tissue cells and ultimately prepares a fertile field for bacterial invasion. It is unfortunate that pseudo-scientific medical articles and vicious advertisements, which are calculated to frighten people into using certain disinfectants, have induced a germ-phobia in the minds of many. Perhaps it is well that many widely advertised mouth washes, douches and sprays are without significant germicidal action when used as directed. The insistence of the partially informed upon germicidal applications places the ethical practitioner in an embarrassing position. As a result, many physicians use bland preparations of slight germicidal efficiency, such as zinc oxide, boric acid or dilute solutions of zinc sulphate. This tends to placate the patient until natural healing can take place. But the continued spraying and douching of the eyes, the nasal cavity or the female genital tract with even the most bland preparations may prove harmful. The introduction of the brilliantly colored medicinal dyes has been fortunate; for while many of these are not germicidal as used clinically, the temporary cosmetic disfigurement they produce is most reassuring to the patient and overcomes his desire to apply compounds which may prove harmful."

Nevertheless, the legitimate therapeutic applications of the antiseptics are many. It is the problem of the physician to choose wisely from the vast number of available drugs and to delineate between the legitimate and harmful uses of bactericides.

Historical. Many drugs were introduced into therapeutics on an empirical basis long before anything was known of their mechanism of action. No more striking example of this fact can be found than by tracing the history of the agents which are now known to be toxic to microorganisms. Centuries before the basic researches of Pasteur, Koch and others established the pathogenicity of bacteria, chemicals were used to control the suppuration of wounds and the spread of contagious diseases. Once the true significance of microorganisms was appreciated, many drugs were already available as germicides, and oddly they represent compounds which rank high in efficiency and are still in use.

The earliest written records of man contain references to the use of germicidal agents. That the ancient Egyptian embalmers had found excellent preservatives among the spices, vegetable oils and gums is attested to by the fine state of preservation of Egyptian mummies. Ancient Persian laws instructed the populace to keep drinking water in bright copper vessels. The practice of salting, smoking and spicing foods is older than recorded history. The Bible cites many public health measures among which are the purification of houses of the sick and the anointing of lepers and others. The use of wine and vinegar in the dressing of wounds dates back at least to Hippocrates.

During the 19th century, the agents used empirically for their germicidal action included several compounds still employed today. Because it was then believed that there was an association between putrefaction and the spread of disease, chlorine occupied a prominent place due to the fact that it was a deodorant. For example, Semmelweiss decreased the incidence of puerperal fever in the obstetrical ward of the Allgemeines Krankenhaus of Vienna from 11.4 to 1.27 per cent by ordering the medical students (who were prone to come directly from the autopsy room to the obstetrical ward) to wash their hands in chlorinated lime before examining patients. In addition, agents such as silver nitrate and iodine were advocated for the treatment of gonorrhea. Following the introduction of the technic of aseptic surgery, the use of iodine, carbolic acid, mercuric chloride and many other drugs became widespread.

The development of the technic for culturing microorganisms provided not only a great impetus but also an indispensable tool for chemotherapeutic research on bactericidal drugs. Ingenious but none too accurate methods were soon introduced to compare the germicidal actions of various compounds, and it is interesting to note that many of the present misconceptions as to the value of certain of the older bactericidal drugs had their origin in these early experiments. However, by 1903 the technic for determining phenol coefficients was developed by Rideal and Walker and some degree of order was introduced into the field. Even today the problem of evaluating the germicidal activity of chemical agents is far from standardized. The number of variables which must be controlled is apparently too great to permit uniformity of results. The problem is further complicated by the difficulty in determining the toxicity of germicidal drugs for tissue cells. For these reasons it is often impossible to state with certainty that one bactericide is definitely superior to another, and probably this fact, more than any other, accounts for the needlessly large number of agents which have been introduced for therapeutic use. In the following discussion, approximately 100 drugs are considered, and these represent a selection which is limited largely to official or Council-accepted preparations. That some of these compounds are superior to others is obvious. However, a critical evaluation of each drug in relation to the others is as yet impossible with the present methods available for comparison. Those agents which have outstanding superiority or which have toxicological importance will be described in some detail.

Terminology. The terminology used to describe the actions of drugs on microorganisms is unfortunately somewhat confusing due to the discrepancy between the strict definition of the terms employed and their usage in loose medical parlance. There can be little confusion concerning the meaning of *disinfectant, germicide, bactericide, fungicide, treponemicide, trypanocide, viricide,* etc. All refer to drugs which are capable of killing various types of organisms. However, the term *antiseptic* has been widely misused. The word comes from the Greek *anti septikas* (against rotting) and was employed long before bacteria were known. In a bacteriological sense, it refers to an agent which inhibits the growth of bacteria. The layman, however, usually considers the term antiseptic to be synonymous with bactericide and disinfectant and is often misled by unsupported commercial advertising claims. In fact, the Federal Food and Drug Law of 1938 contains a clause stating that antiseptics must possess germicidal properties. This assures the dispensing of potent agents, but does not help the problem of terminology.

Properties Desirable in Germicides. There are many properties which must first be considered before the clinical value and applicability of a particular germicide can be determined.

Germicidal Potency. Obviously the more toxic a compound is to microorganisms, the more valuable it is as a germicide. However, the impression must not be gained that the drug which kills organisms in the highest dilution is necessarily the best therapeutic agent. Weighed against germicidal potency should be the toxicity for the tissue of the host. Therefore, an adequate statement of bactericidal efficiency should include information concerning tissue toxicity and should be based upon the resulting therapeutic index. It is difficult to measure tissue toxicity. Salle and coworkers (1935, *et seq.*) have approached the problem by determining the weakest concentration of the compound under examination which inhibits the growth of embryonic tissue. An interesting and revised ranking of the therapeutic efficiency of various antiseptics and germicides is obtainable by this technic.

A compound may have a high bactericidal potency in an environment optimal for its action but its efficacy may be markedly inhibited by extraneous substances. For this reason, many drugs active *in vitro* are relatively inactive under the conditions encountered in the body. For example, silver nitrate is inactivated by the chloride ion, and chlorine antiseptics lose much of their efficiency in the presence of organic matter. Certain compounds are adversely affected by an unfavorable pH. Thus, mandelic acid is an effective urinary antiseptic only in a highly acid medium. In the final determination of the germicidal potency of a drug, the conditions which are met in the body must be considered.

Specificity of Action. At times it is desirable that a germicide be highly specific for a certain organism, but under other circumstances a more general type of antiseptic action may be desired. In general, when treating a mixed infection it is best to use an agent which is active against a variety of organisms. On the other hand, in treating a specific infection it suffices to employ a compound which is selectively toxic for the etiological agent. So marked is the specificity of action of certain germicides that they may be employed in bacteriological technic for the purpose of isolating in pure culture a single organism which is uniquely resistant to the particular drug employed.

Physical and Chemical Properties. It is often desirable that a bactericide have a low *surface tension.* Fluids of low surface tension spread readily, permeate freely and gain ready access to the surface of the bacterial cell. A high *temperature coefficient* may or may not be desirable depending upon the particular purpose for which a compound is being employed. *Esthetic factors* such as odor, color or staining qualities are sometimes determinants in the choice of germicide. For example, certain hospitals do not employ the antiseptic dyes for the treatment of extensive burns because of the economic problem of laundering the soiled linen. *Chemical stability* is another desirable feature, especially in a household germicide which may be used but infrequently.

Speed of Action. Speed and duration of action often determine the usefulness of a germicidal agent. Some substances depend upon the intervention of a chemical reaction before they become actively bactericidal. Others are immediately effective. In the sterilization of the skin prior to a surgical procedure it is essential that a compound have an immediate onset of action. In antiseptics employed for suppurating wounds or chronic skin infections, a sustained action is more to be desired.

Mechanisms of Bactericidal Action. There are a variety of mechanisms by which drugs are toxic to microorganisms. The majority of the nonspecific germicides act by *precipitating the protein* of the bacterial protoplasm. Outstanding agents of this type are phenol and mercuric chloride. In general, it can be stated that germicides which act by precipitation are also toxic to the tissues of the host. Other compounds act by *combining chemically with some constituent of the bacterial protoplasm.* This may be a rather specific type of action such as that which characterizes the reaction of the basic dyes with Gram-positive organisms, or it may be nonspecific as exemplified by the combination of chlorine with the amino groups of the bacterial protoplasm. Compounds of this type in certain instances have high therapeutic indices. Many bactericides act by virtue of their *oxidizing* properties. Outstanding examples are the peroxides, perborates and permanganates. Other agents may interfere with the oxidations taking place within the bacterial cell. Mapharsen, which is occasionally employed locally as a treponemicide, probably acts in this manner. Strong mineral acids or alkalis *hydrolyze* bacterial protoplasm but are also so toxic to tissue cells that they can only be used as cauterants. Lastly, in many instances the mechanism of bactericidal action is unknown. For example, no ready explanation is available to account for the fact that certain non-ionized organic mercury-containing compounds are far more toxic to bacteria than the highly ionized mercuric chloride.

Classification. In a study of such a heterogeneous group of compounds as comprise the antiseptics, germicides and parasiticides, some method of classification is desirable. So varied are the compounds with respect to chemical structure, mechanisms of action and therapeutic uses, however, that too strict a classification may be more confusing than elucidating. If grouped on the basis of their therapeutic applications, most of the compounds could be included under several categories. The difficulty of an attempt to classify the drugs with respect to mechanism of action is that in some instances this is not known, and in others a single compound may act in more than one manner. Thus, by elimination, a chemical classification is the least objectionable. The following table indicates the drugs which are discussed and the sequence in which they are considered. As can be seen, even a strict chemical classification cannot always be adhered to.

Phenols, Cresols, Resorcinols and Related Compounds.

Phenol, substituted phenols, cresol, cresatin, creosote, guaiacol, resorcinol, hexylresorcinol, thymol, pyrogallol, picric acid, tars.

Alcohols.

Aldehydes.

Formaldehyde, methenamine.

Acids.

Inorganic acids, benzoic acid, acetic acid, boric acid, salicylic acid, mandelic acid.

Halogens and Halogen-Containing Compounds.

Iodine, iodoform, sodium hypochlorite, chlorinated lime, chloramine-T, dichloramine-T, azochloramid, halazone.

Oxidizing Agents.

Hydrogen peroxide, sodium peroxide, calcium peroxide, zinc peroxide, sodium perborate, potassium permanganate, zinc permanganate, potassium chlorate.

Heavy Metals and Derivatives.

Mercury, mercuric chloride, miscellaneous ionizable mercury salts, mercurochrome, merbaphen, meroxyl, merthiolate, silver, silver nitrate, silver lactate, silver picrate, strong protein silver, mild protein silver, silver halides, zinc chloride, zinc sulfate, zinc oxide, zinc stearate, copper, copper sulfate.

Dyes

Azo dyes—scarlet red, dimazon, pyridium; acridine dyes—acriflavine, proflavine; fluorescein dyes; phenolphthalein dyes; triphenylmethane dyes—gentian violet, crystal violet, methyl rosaniline, brilliant green; miscellaneous dyes—methylene blue.

Miscellaneous.

Sulfur, ichthammol, chrysarobin, dioxyanthranol, betanaphthol, balsams, volatile oils.

PHENOLS, CRESOLS AND RESORCINOLS

Phenol

Phenol (carbolic acid) is the oldest of the antiseptics, having been introduced by Lister in 1867. It is mainly of historical interest, for today it is seldom employed clinically. However, phenol is still used as a standard of comparison for other germicidal compounds, and the *phenol coefficient* is employed as a measure of the bactericidal activity of compounds in comparison with phenol under standard conditions of examination. Many antiseptics, when tested against certain organisms, have phenol coefficients of over a thousand (*i.e.,* are effective in concentrations less than one-thousandth that of phenol). When this fact is considered in conjunction with the high toxicity of phenol, it is easily understood why carbolic acid is no longer employed in therapeutics.

Pharmacological Actions. Both the local and systemic actions of phenol are of practical importance.

Local Actions. Phenol is a "general protoplasmic poison." In high concentrations the compound is a protein precipitant, but in more dilute solutions proteins are denatured without being coagulated. The protein-phenol complex is not a firm one, as is, for example, the combination of protein and heavy metal. Consequently, phenol escapes from its combination with denatured or precipitated protein and therefore has great penetrability in tissues.

Phenol is toxic to all types of cells. In adequate concentrations it is both bactericidal and fungicidal. The compound also has a markedly toxic action on tissues, and because of its great penetrability affects even the unabraded skin. When applied directly to the skin, a white pellicle consisting of precipitated protein is formed. This soon turns red and eventually sloughs, leaving the cutaneous surface stained a light brown. If phenol remains in contact with the skin, it penetrates into the deeper tissues and extensive gangrene may occur.

Phenol is bacteriostatic in concentrations of approximately 1:500. However, a strength of more than one per cent is required before the common bacteria are killed. Spores and viruses are even more resistant to phenol. The bactericidal efficiency of phenol is greatly reduced by cold and an alkaline medium. Also the drug is much more effective in aqueous solution than it is in glycerin or fats. Phenol is fungicidal in dilutions of 1:75.

When applied locally, phenol penetrates to the sensory nerve endings and consequently has a local anesthetic action. A five per cent solution, even when applied to an unabraded epithelial surface, produces a feeling of warmth and tingling and eventually rather complete local anesthesia. When phenol in this concentration comes in contact with exposed tissue or mucous membranes, it precipitates proteins, is markedly irritating before anesthesia sets in, and may cause extensive tissue necrosis.

Systemic Actions. These may all be classified as toxic. Phenol has a marked action on the central nervous system. In animals there is evidence of stimulation manifested in muscle tremors and eventually convulsions. The site of action is largely on the spinal cord, but extends to the medulla and higher centers. Stimulation is soon followed by depression and death results from respiratory failure. In man little central stimulation is observed and the prominent effects are those of central depression.

The circulation is also markedly depressed by phenol. The blood pressure falls as a result partly of central vasomotor depression but mainly due to a direct toxic action of phenol on the myocardium and on the finer blood vessels.

Phenol is a powerful antipyretic. The fall in body temperature probably results from a central action on the hypothalamus. The mechanism by which phenol produces a fall in body temperature is not unlike that of the salicylates.

Absorption, Fate and Excretion. Phenol gains ready access to the body from all sites of administration and can even reach the circulation when applied directly to the intact skin. A portion of the absorbed drug is oxidized to hydroquinone and pyrocatechin. The remainder is excreted either unchanged or conjugated with glycuronic and sulfuric acids. When the urine is exposed to air, further oxidation occurs and imparts to the urine a dark "smoky" color.

Preparations. *Phenol,* U.S.P., B.P., is composed of colorless crystals with a characteristic somewhat aromatic odor, and is soluble in water to the extent of one part in 15. Despite the fact that phenol is little used in therapeutics, a number of preparations remain official *Liquefied Phenol,* U.S.P., B.P. (Liquefied Carbolic Acid), is phenol maintained in a liquid state by the presence of 10 per cent (B.P., 20 per cent) of distilled water, thus allowing greater ease for dispensing. *Phenol Ointment,* U.S.P., consists of two per cent phenol in yellow wax and petrolatum (B.P., two per cent in ointment base). N.F. preparations consist of *Phenolated Water* (two per cent aqueous solution), *Phenolated Oil* (five per cent in olive oil), *Camphorated Phenol* (30 per cent phenol and 60 per cent camphor in liquid petrolatum), *Glycerite of Phenol* (20 per cent in glycerin), *Phenolated Solution of Iodine* (1.5 per cent compound solution of iodine and 0.6 per cent phenol in glycerin and water), and *Phenolated Lotion of Calamine* (Compound Lotion of Calamine) in which one per cent phenol is added to Calamine Lotion.

Phenol Poisoning. Phenol is rather commonly used for suicidal purposes. In the past, poisoning also frequently resulted from the wide use of phenol as an antiseptic. When taken orally, phenol produces extensive local corrosion which leads to severe pain and vomiting. Shock, due to widespread capillary injury, and death may rapidly ensue. After absorption, phenol may produce fleeting excitement, but usually the patient rapidly lapses into unconsciousness. The blood pressure is low, cold sweat is prominent, the body temperature falls markedly, urine is scanty and contains albumin, casts and free hemoglobin, and death results from respiratory failure.

Treatment. The main objective in the therapy of phenol poisoning is to remove the agent from the stomach before extensive absorption has occurred. A stomach tube should be passed immediately and a lavage fluid should be employed which dissolves phenol and yet does not hasten absorption. Goodman and Geiger (1935) have shown experimentally in animals that olive oil is well suited for this purpose. Alcoholic solutions or mineral oil should be avoided. The former effects the solution of phenol but also facilitates gastric absorption; the latter is relatively ineffective in dissolving phenol. After copious lavage, a portion of clean oil should be left in the stomach to retard subsequent absorption of phenol and to act as a diluent and demulcent. Treatment of systemic symptoms is purely symptomatic. The patient should be kept warm. Shock therapy should be instituted when indicated. The administration of copious amounts of isotonic sodium chloride solution promotes diuresis and protects the kidneys to some degree. Central nervous system stimulants are of little value, but artificial respiration may prove helpful. The practice of giving sodium sulfate with the purpose of hastening the formation of the non-toxic phenolic sulfates is obsolete and without experimental substantiation. The toxic dose of phenol for adults has been estimated to be from eight to 15 grams. In fatal cases, death usually results within 24 hours or less but the prognosis should be guarded even after this period of time has elapsed.

If phenol has been applied locally to skin or mucosae, it can be effectively removed with 50 per cent alcohol or with castor oil.

Therapeutic Uses. Phenol has few legitimate uses as an antiseptic. In full strength, a few drops of liquefied phenol may be employed to *cauterize* small wounds, dog bites, snake bites, etc. It is commonly employed as an antipruritic, either in the form of compound lotion of calamine or as an ointment or simple aqueous solution. Aqueous solutions stronger than two per cent, however, should not be applied to the surface of the body. In heavy glycerin, four per cent solutions may be employed if necessary. Phenol has been used for *sclerosing* hemorrhoids, but more effective and less dangerous substances are available. Crude carbolic acid is sufficiently inexpensive to use for *disinfection* of excrement.

Substituted Phenols

Relation of Chemical Structure to Pharmacological Action. A number of phenol derivatives have greater bactericidal activity than phenol itself. The most important of these are the *halogenated phenols,* the *alkyl substituted phenols* and the *resorcinols.*

The antiseptic activity of the halogenated phenols varies with the halogen introduced into the benzene ring, its position in the ring and the number of substitutions effected. The order of increasing activity with respect to the particular halogen introduced is as follows: chlorophenols, bromophenols and iodophenols. The monohalogenated phenols are most antiseptic when the halogen is in the meta position, and least active when the substitution is made in the ortho position. Also a dihalogenated compound is more potent than a monohalogenated derivative and in turn a trihalogenated phenol is still more active. For practical purposes, however, these halogen derivatives are of little value, for their solubility in water decreases as their bactericidal property increases. The most active compounds are too insoluble to be therapeutically useful. The fungicidal activity of the halogenated phenols runs parallel to the bactericidal activity.

The *nitration* of phenol also increases its bactericidal activity. The resultant compounds, however, assume many new properties. For example, 2–4 dinitrophenol is a powerful metabolic stimulant and is never employed as an antiseptic. Trinitrophenol (picric acid) is an effective but toxic antiseptic.

Of the various *alkyl derivatives* of phenol, the *cresols* are the most important. Cresol is merely phenol with a methyl group added in the benzene ring. There are three such compounds, ortho, meta and para cresol, depending upon the position of substitution. The three cresols differ little in their antiseptic properties, and in general it may be stated that they are about three times more bactericidal than phenol. Substitution of other alkyl groups than the methyl group in the phenol molecule greatly increases activity. For example, the phenol coefficients against *E. typhi* of para-alkyl substituted phenols are as follows: methyl phenol (cresol), 2.5; ethyl phenol, 7.4; propyl phenol, 21.6; butyl phenol, 68.0; amyl phenol, 197; hexyl phenol, 500 (Schaffer and Tilley, 1927).

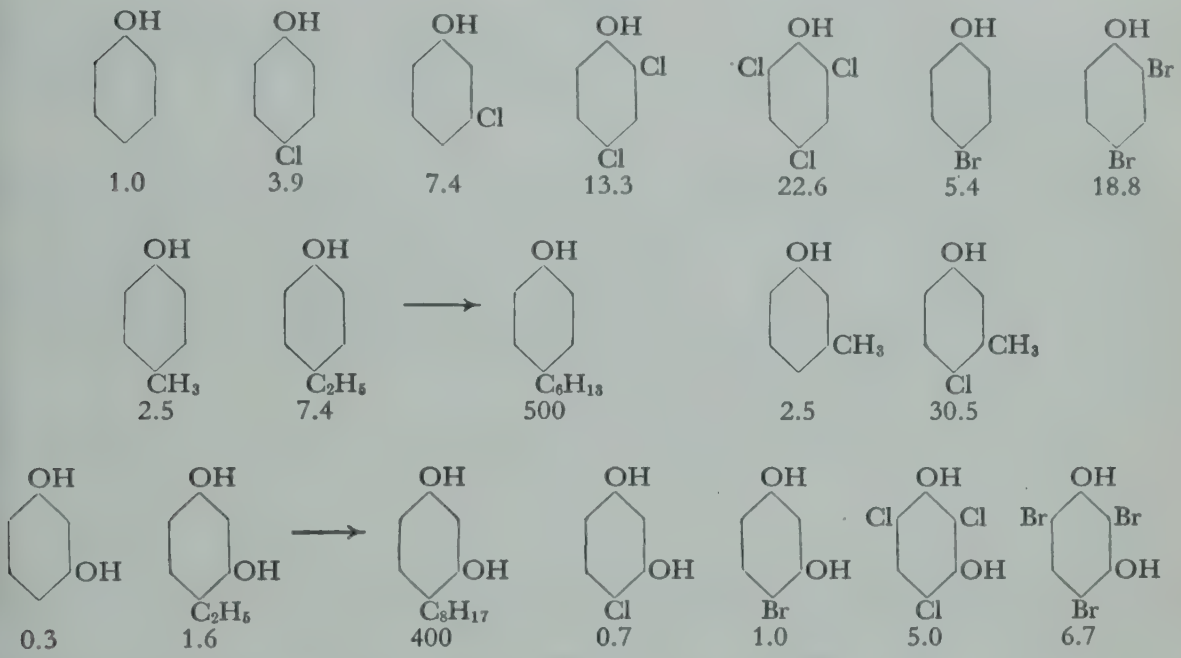
The higher homologues of cresol in which two or more methyl groups have been substituted in the phenol molecule are also more active than the simple cresols. This group of compounds is generally referred to as *cresylic acid derivatives.* Also the addition of aromatic groups enhances the action of phenol. Thus phenylphenol is a powerful germicide. The halogenation of substituted phenols increases their antiseptic power still further. The poor solubility of most of these compounds, however, greatly diminishes their usefulness.

The *resorcinols* also have definite bactericidal action which can be greatly enhanced by certain substitutions in the molecule. Chemically, resorcinol is phenol with an additional OH group in the meta position. Resorcinol itself is only about one-third as bactericidal as phenol, but if alkyl substitutions are made para to one of the hydroxy groups, the antiseptic activity of the resulting compounds increases with the length of the substituted chain. Also, halogenation of resorcinol derivatives increases bactericidal power. The relationship between chemical structure and antiseptic potency of the phenol derivatives is presented in Table 43.

Cresols. As has already been stated, there are three different cresols of approximately equal antibacterial activity. Cresol is usually marketed as a mixture of the three forms. Cresol is no more toxic than phenol and is about three times as active. It therefore has a higher therapeutic index and is used more extensively than phenol. Cresol is a fairly efficient bactericide against the common pathogenic bacilli, including acid-fast organisms. It is slightly less active against cocci. Spores are killed only after long exposure to high concentrations. Cresol is more toxic to viruses than is phenol.

TABLE 43

RELATION BETWEEN CHEMICAL STRUCTURE AND BACTERICIDAL ACTIVITY OF PHENOL DERIVATIVES



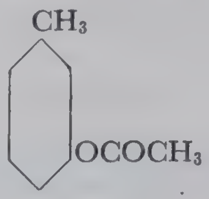
Numbers below the formulas are the phenol coefficients obtained by testing the compounds against *E. typhi* in the absence or organic matter. (Data of various investigators as presented by McCulloch, 1936.)

The systemic action of cresol is almost identical with that of phenol and does not warrant separate discussion. The same holds true for the absorption, fate and excretion of cresol and the symptoms and treatment of cresol poisoning. It should be remembered that cresol is just as toxic as phenol and cresol preparations should not be used with a false sense of security. Many cases of poisoning from cresol have been reported.

Preparations. Cresol, U.S.P., B.P., is a mixture of isomeric cresols. It is a colorless or yellowish liquid which turns dark brown upon exposure to air. Cresol is soluble in water only to the extent of one part in 60. Therefore it is commonly used in the form of *Saponated Solution of Cresol* (Compound Solution of Cresol), U.S.P. (*Solution of Cresol with Soap,* B.P. [Lysol]). This consists of 50 per cent cresol in saponified linseed oil. In this form it is miscible with water. There are many proprietary cresol preparations on the market, the names of which give no indication of their composition. Extravagant claims are made for these preparations and they are sold at exorbitant prices.

Therapeutic Uses. Compound solution of cresol is widely used for disinfecting inanimate objects. It is cheaper than and superior to phenol. It is probably the preparation of choice for the disinfection of excrement. Also it may be employed as a hand wash in a concentration of two per cent. A 1:500 solution of compound solution of cresol is sometimes used as a mildly antiseptic vaginal douche. Proprietary preparations are widely advertised for this purpose.

Cresatin, N.N.R. This compound is the acetic acid ester of metacresol and has the following structural formula:



Cresatin

It is claimed that the acetylation of the phenolic OH diminishes the toxicity of the compound. Cresatin is said to possess both antiseptic and local anesthetic properties. It is especially recommended for infections of the ear canal, nose and throat. It is applied pure, or diluted with alcohol or oils.

Creosote. Creosote is a mixture of phenols obtained from wood tar. It consists mainly of creosol and guaiacol (page 818). The bactericidal potency of creosote varies with different samples but in general is about two to three times that of phenol. *Creosote,* U.S.P., B.P., and *Creosote Carbonate* U.S.P., are used infrequently as antiseptics, but rather are employed as expectorants (page 819). Creosote is used in the preserving of wood.

Guaiacol. This compound is also used more often as an expectorant than as an antiseptic, although it possesses bactericidal properties. Its pharmacology is discussed on page 818.

Resorcinols. Resorcinol, like phenol, is both bactericidal and fungicidal but is only about one-third as active. Locally, resorcinol is a protein precipitant. After absorption, the compound resembles phenol in its systemic actions. It is antipyretic and in toxic doses stimulates and then depresses the central nervous system. Central stimulation is more prominent than is the case with phenol.

Preparations and Therapeutic Applications. Resorcinol, U.S.P., B.P., is a colorless crystalline substance freely soluble in water, alcohol, and various organic solvents. Resorcinol is widely used in the treatment of such conditions as *ringworm, eczema, psoriasis, seborrheic dermatitis,* etc. It is usually employed as an ointment or lotion in strengths varying from one to 10 per cent. A five per cent concentration is most commonly employed.

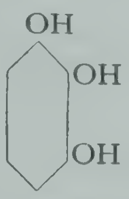
Hexylresorcinol. It was pointed out that the substitution of alkyl groups in the resorcinol molecule greatly increases bactericidal activity. Hexylresorcinol was introduced as a urinary antiseptic in 1924 by Leonard and coworkers. Under ideal conditions it is highly bactericidal. Much of the bactericidal efficiency of the drug is due to the low surface tension of its solutions and in the presence of organic matter the compound is much less effective.

Therapeutic Uses as an Antiseptic. Hexylresorcinol has the advantage of being odorless and stainless. It is marketed as a 1:1000 solution in glycerin and water. It is employed as a general antiseptic but the drug is quite irritating to tissue and an occasional individual exhibits marked sensitivity to its local application (Cummer, 1933; Walter, 1935).

Hexylresorcinol was advocated as an efficient *urinary antiseptic.* About one-third of the orally ingested drug is absorbed and excreted in the urine. However, much of the excreted portion is in a conjugated form which greatly impedes its action. Sulfanilamide, mandelic acid and methenamine are much more efficient antiseptics for the urinary tract.

Hexylresorcinol is an efficient anthelmintic against certain parasites. The pharmacology of the drug is discussed in greater detail in this connection.

Pyrogallol. *Pyrogallol* (Pyrogallic Acid), U.S.P., is a trihydroxybenzene having the following structural formula:



Pyrogallol

The compound occurs as a white, odorless, crystalline powder, soluble in water and organic solvents. It is a powerful reducing agent which possesses significant fungicidal power, but its toxic properties preclude its wide use. If absorbed, pyrogallol is toxic to red blood cells and the kidney. The corpuscles are fragmented and large amounts of methemoglobin are formed. Renal injury is manifested by the presence of albumin, red blood cells, and casts in the urine.

Pyrogallol is usually employed in ointment form in the strength of five or ten per cent. It is used in the treatment of *ringworm, psoriasis, lupus erythematosus* and other skin disorders. Because of the dangers of poisoning, the drug should not be employed if an extensive area of the skin requires medication. The drug stains the skin brown.

Thymol. Thymol is an alkyl derivative of phenol. The structural formula, general pharmacology, preparations and use of thymol as an anthelmintic are presented elsewhere. Thymol also possesses bactericidal and fungicidal properties. As a bactericide, the compound is more active than phenol against pathogenic cocci, but is less active against Gram-negative bacteria. The chief value of thymol, however, is in its fungicidal properties. Myers and Thienes (1925) observed that thymol is efficacious in controlling dermatitis caused by pathogenic yeasts. The compound is also destructive to pathogenic fungi.

Thymol has been found to be of clinical value in the treatment of *epidermophytosis.* It may be used in alcoholic solution in the strength of one per cent, and in this vehicle may be incorporated with one per cent oil of cinnamon or three per cent salicylic acid (Wise and Wolf, 1936). Thymol may also be incorporated in dusting powders for the treatment of *ringworm,* a concentration of two per cent in a base of 35 per cent boric acid and equal amounts of zinc oxide, talc and zinc stearate being an efficacious mixture. The drug is also employed in keratolytic ointments such as Whitfield's ointment.

Thymol is one of the very few drugs which is effective in the treatment of *actinomycosis.* For skin lesions, both local and oral therapy with thymol are employed, and combined with surgical measures when these are indicated. The oral dose is 1.5 grams of thymol daily in divided portions two of every three days. The drug is conveniently administered in capsules. For the treatment of skin lesions, it may be necessary to open the sinuses widely and fill them with 10 per cent thymol in olive oil (*see* Myers, 1937; Joyce, 1938).

Pulmonary actinomycosis has also been successfully treated with thymol. The dose is two grams daily. In addition, the drug is worthy of trial in the treatment of *pulmonary moniliasis, blastomycosis,* and *coccidioidal granuloma.*

Thymol Iodide. *Thymol Iodide,* U.S.P., is a mixture of iodine derivatives of thymol, and consists principally of dithymol-diiodide. The compound is a water-insoluble reddish-brown bulky powder containing 43 per cent iodine, and it is used as an *antiseptic dusting powder.* Thymol iodide is similar to iodoform in its properties. It is sometimes employed in ether solution, in which form it has been used successfully in the concentration of 25 per cent for the treatment of *chancroid ulcer.*

Picric Acid. Picric acid is 2–4–6–trinitrophenol. It is both germicidal and anesthetic and acts by virtue of its property as a protein precipitant. Picric acid finds special usefulness in the treatment of burns and exudative wounds. For this purpose it is employed as a one per cent aqueous solution. It also has been used in combination with alum as an astringent nasal spray for the prophylaxis of poliomyelitis, but it is more dangerous for this purpose than are the zinc salts. Picric acid is employed in a five per cent alcoholic solution for the treatment of such skin disorders as the vesicular stage of *epidermophytoses, eczema,* etc.

Picric acid is a systemic poison and extensive absorption leads to toxic symptoms. It therefore should be used with caution when applied to denuded skin areas and should not be employed for the treatment of extensive burns. The drug hemolyzes red blood cells, causes acute hemorrhagic glomerular nephritis and acute liver damage. Death may result from anuria. In severe acute poisoning with picric acid, the central nervous system may be depressed and symptoms of headache, progressive stupor and coma occur. Death may follow. If the drug is ingested orally, severe gastro-enteritis with nausea and vomiting results. The vomitus is stained a deep yellow. Locally, high concentrations of picric acid may give rise to a dermatitis known as "picric itch." Severe pruritus, vesicle formation, edema, and an acute weeping eczema characterize the local lesions. The *treatment* of picric acid poisoning is purely symptomatic. The systemic measures used should include gastric lavage and the transfusion of blood. Eczematoid skin lesions are treated as any other acute eczema.

Trinitrophenol (Picric Acid), U.S.P., B.P., is the official preparation. It consists of pale yellow crystals soluble to the extent of 1:78 in water and 1:12 in alcohol. Picric acid forms intensely yellow solutions which stain the skin. The stains can be removed with potassium sulfate powder or magnesium carbonate paste. Picric acid explodes if heated rapidly or percussed. *Butesin Picrate,* N.N.R., is an ointment which combines the antiseptic action of picric acid with the anesthetic properties of butesin.

Tars

The tars are obtained from the destructive distillation of various woods and coal and consist mainly of cresols and guaiacols. When suitably diluted, tars act as mild irritants and antiseptics and are employed in the treatment of diseases of the skin. Tar occurs as a thick viscous fluid having an empyreumatic, terebinthinate odor. Official preparations include *Pine Tar,* U.S.P. (*Tar,* B.P.), *Juniper Tar* (*Oil of Cade*), U.S.P., B.P., and *Coal Tar,* N.F. The tars are usually prescribed in ointment form. Official ointments include *Pine Tar Ointment,* U.S.P. (50 per cent pine tar) and *Ointment of Coal Tar,* N.F. (five per cent coal tar in paste of zinc oxide). The tars are employed in the treatment of diseases of the skin such as *psoriasis* and *eczema-dermatitis.* The official pine tar ointment is seldom used in full strength, but is usually diluted about four times.

ALCOHOLS

The aliphatic alcohols are germicidal in varying degree, the alcohols of higher molecular weight being much more active in this regard. The phenol coefficients of the primary alcohols increase progressively through the series from 0.026 for methyl alcohol to 21.0 for octyl alcohol. Secondary alcohols are less bactericidal and tertiary alcohols have still less activity.

Ethyl alcohol is the only one of the alcohols which is extensively employed for its antiseptic action. Although often inefficient, especially against spores, it is widely used, particularly for the disinfection of the skin and inanimate objects such as instruments, ampules, etc. The antiseptic properties and uses of ethyl alcohol are discussed elsewhere.

ALDEHYDES

Several of the aldehydes possess bactericidal activity. Of these, formaldehyde, the simplest of the aliphatic aldehydes, is by far the most active, and in this respect the aldehydes contrast sharply with the alcohols. Formaldehyde is the only member of the series which is employed in medicine.

Formaldehyde. Formaldehyde is a gas at room temperature. In this state it has been extensively employed in the past for the purpose of fumigation. Formaldehyde is infrequently used for this purpose at present, and indeed the practice of fumigating rooms for the purpose of killing bacteria is probably an impractical procedure.

Preparations. Formaldehyde is readily soluble in water and is employed in the form of aqueous solutions. The U.S.P. and B.P. preparation is known as *Solution of Formaldehyde* (formalin). It contains 37 per cent by weight of formaldehyde to which is added methyl alcohol to prevent polymerization and inactivation.

Local Actions. Locally, formaldehyde acts as an irritant and "general protoplasmic poison." The compound is toxic to protoplasm for two reasons. In high concentrations it is a protein precipitant and both preserves and hardens tissue. Thus formalin is a useful fixing fluid in histological technic. However, concentrations which do not precipitate protein are also toxic to cells, probably because of the high chemical reactivity of formaldehyde with proteins. For example, the reaction between formaldehyde and the free amino groups of protein structures is the basis of the well-known *formol titration,* and such a reaction may account for the bactericidal properties of the compound.

Formaldehyde, in proper concentration, is an effective germicide against all forms of organisms. In a concentration of 1:200 it kills both spore-forming and non-spore-forming organisms only after six to 12 hours. In this concentration the drug also sterilizes saccharolytic anaerobes within 48 hours and the proteolytic anaerobes within 96 hours. Higher concentrations are more rapidly effective. Formaldehyde is toxic to tubercle bacilli and inasmuch as it loses little of its effectiveness in the presence of organic matter it is widely employed to sterilize sputa. Formaldehyde solutions are also viricidal.

Formaldehyde possesses valuable detoxifying properties. It is capable of converting toxins to toxoids, the latter retaining the ability to elicit typical antigenic responses. Therefore the drug is of value in the preparation of non-toxic antigens, such as diphtheria toxoid. The chemical reactivity between formaldehyde and the amino groups of proteins has been suggested as an explanation of the detoxifying action.

Formaldehyde is too irritating to be applied to body tissues in effective concentrations and finds its widest use in the disinfection of inanimate objects such as surgical instruments and gloves (two to five per cent), excreta (10 per cent), brush bristles (10 per cent), etc. A unique application is for the sterilization of the eggs of flesh flies employed to produce sterile maggots for surgical use (five per cent solution of formaldehyde plus one per cent sodium hydroxide to prevent agglutination). Formaldehyde has been employed in dilute solutions as a vaginal douche, in ivy poisoning and in fungus infections of the skin. Solution of formalde hyde has also been used as a skin astringent and hardener (20 to 30 per cent strength) in the treatment of hyperhidrosis. Repeated contact with solutions of formaldehyde may cause an eczematoid dermatitis.

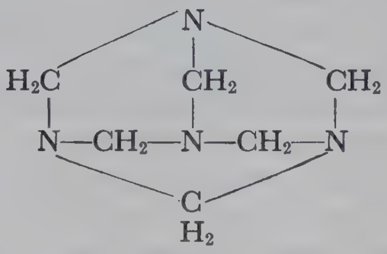
Systemic Actions. The systemic actions of formaldehyde may all be classified as toxic. Exposure to the gas leads to intense irritation of the eyes and respiratory tract. Conjunctivitis, coryza, bronchitis and even pneumonia may result. If a solution of formaldehyde is ingested, the mucous membranes of the mouth, throat and intestinal tract are irritated and severe pain, vomiting and diarrhea result. After absorption, formaldehyde depresses the central nervous system and symptoms not unlike those of alcoholic intoxication are noted. These consist of vertigo, depression and coma. Rarely convulsions are observed. Formaldehyde is oxidized to formic acid and a severe acidosis may result. The urine is scanty and may contain red blood cells and casts.

Treatment of poisoning is mainly symptomatic. Acidosis must be combated. Additional measures include copious gastric lavage and the administration of demulcents for orally ingested solutions, central nervous system stimulants if depression is severe, and shock therapy if indicated.

Methenamine

Methenamine, a urinary antiseptic, is active by virtue of the fact that in acid solution it slowly releases formaldehyde. Methenamine was first prepared by Butlerow (1860). It was introduced into therapeutics for the treatment of cystitis by Nicolaier (1894) and in 1899 this same investigator demonstrated that its efficacy was related to the liberation of formaldehyde in the urine.

Chemistry, Absorption, Fate and Excretion. Methenamine is a condensation product of formaldehyde and ammonia and has the following structural formula:



Methenamine

The drug is absorbed as such from the intestinal tract, circulates in body fluids in an unchanged form and is rapidly excreted in the urine. If the urine is acid, formaldehyde is released as a result of the following reaction:

$$N_4(CH_2)_6 + 6H_2O \xrightarrow{\text{acid}} 4NH_3 + 6HCHO$$

Relation Between Activity and pH. The fact that methenamine releases formaldehyde only in an acid medium was demonstrated independently by Hinman (1913) and Hanzlik and Collins (1913). Shohl and Deming (1920) investigated this point further and showed that both *in vivo* and *in vitro* there is a quantitative relationship between the pH of the urine and the amount of formaldehyde liberated. They found that the percentage of the theoretical amount of formaldehyde liberated from methenamine bore the following relationship to urinary pH: pH 5.0, 20 per cent; pH 5.4, 13 per cent; pH 5.8, eight per cent; pH 6.4, three per cent; pH 7.6, zero per cent. All workers are not agreed, however, that such a quantitative relationship exists, for there is evidence that formaldehyde may form inactive combinations with certain organic constituents in the urine and its effective concentration may thus be materially diminished.

Bactericidal Activity. It is probable that the bactericidal activity of formaldehyde in the urine has been overestimated. The literature on this subject is highly controversial. For example, the limiting concentration for bactericidal action has been placed anywhere from 1:5000 to 1:30,000. In a carefully conducted investigation, however, Vermooten and Berry (1933) present evidence that in concentrations as high as 1:3000 formaldehyde is only bacteriostatic rather than bactericidal even after several hours' exposure of the organisms. This can be demonstrated if cultures exposed to formaldehyde are centrifuged and washed before plating so that no formaldehyde is transferred to the culture medium.

Preparation, Dose and Mode of Administration. *Methenamine* (*Hexamethylenamine, Hexamethylenetetramine*), U.S.P. (*Hexamine,* B.P.), is a white, odorless, water-soluble powder with a sweetish taste. It is also known under various trade names such as urotropin, formin, cystamin, cystogen, urisol, uritone, aminoformaldehyde, etc., but should be prescribed by its official title.

The U.S.P. dose of methenamine is 0.3 gram, but the effective dose is much higher, usually being four to five grams daily. Inasmuch as excretion is rapid the drug is administered in four equal doses in order to obtain a fairly constant concentration in the urine. An acid-forming salt such as sodium acid phosphate, ammonium nitrate, or ammonium chloride should also be given (five to eight grams daily) to produce the proper urinary pH. The sodium biphosphate should be administered midway between the doses of methenamine. As an added assurance the urine should be tested with methyl red, chlorphenolred or nitrozene indicator paper. Approximately 10 to 30 per cent of the administered methenamine is converted to formaldehyde by the acid stomach contents. This can be avoided by the use of enteric-coated preparations. The remainder is excreted in the urine and the above dose produces a urinary concentration of formaldehyde of approximately 1:5000 provided the urine is sufficiently acid and the 24-hour urine volume is approximately 1200 cc. The drug is usually given for one week to two or more weeks.

Therapeutic Uses. Methenamine was formerly one of the most effective of urinary antiseptics available, but it has largely been replaced by sulfanilamide and mandelic acid. It is of special value in patients suffering from renal insufficiency for unlike mandelic acid, the drug is non-toxic if unexcreted. It also has a special usefulness in resistant urinary infections where it is highly desirable to change from one drug to another in order that the bacteria do not become markedly resistant to a specific agent. Particularly good results may be obtained in the treatment of *E. coli* infections. Coccal infections respond less satisfactorily. Medication with methenamine should be accompanied by frequent urine cultures in order to control dosage and duration of medication. Methenamine is also of value as a prophylactic administered before instrumentation of or operation on the urinary tract. It has also been used in typhoid fever as a prophylactic against bacilluria.

Limitations. There are no specific contraindications to methenamine, but in many conditions for which this drug is prescribed it is absolutely valueless. For example, it was pointed out that methenamine liberates formaldehyde only in an acid medium and that at a neutral or alkaline pH the drug is inert. Therefore it cannot be expected to exert action against organisms that are not in an acid environment and consequently the drug is useless in the treatment of such conditions as infections of the meninges, joints, biliary tract, etc., despite its presence in all body fluids and secretions. Neither is there a clinical or experimental basis for the use of methenamine as a uric acid solvent in the therapy of gout. Also methenamine does not act as a prophylactic in the prevention of such conditions as the nephritis of scarlatina, as has been claimed.

Untoward Reactions. These are uncommon. An occasional patient may suffer from skin rashes or gastro-intestinal upsets. If large amounts of the drug (eight grams daily) are used over extended periods (three to four weeks), bladder irritation, painful micturition, frequency, albuminuria, and gross hematuria are likely to be encountered.

ACIDS

The acids were employed empirically as antiseptic agents long before the concept of microorganisms was introduced into medicine. The use of acids in the preservation of foods, the preparation of pickles and sauerkraut, the preserving of meat with sour milk and the dressing of wounds with vinegar or sour wine are but a few of the many examples that may be cited.

At present, several acids are employed for their germicidal or antiseptic action. It must not be inferred, however, that each owes its activity to the liberation of hydrogen ions. It is true that those acids which readily dissociate are toxic to all protoplasm and therefore are active bactericides. Other acidic compounds, however, have a more selective type of action which apparently is dependent on the molecule as such. The acids are discussed together merely because of their similar type of structure and not because of a common mechanism of action.

Inorganic Acids. The strong inorganic acids are occasionally employed as cauterizing agents for the immediate sterilization of dangerously infected wounds. *Nitric acid* is the one of choice for it forms a firm eschar and does not penetrate too deeply. It is commonly applied in the form of concentrated or fuming nitric acid.

Chromic Acid. Chromic acid is a powerful germicide which combines the actions of an oxidizing agent, a heavy metal and an acid. It is extremely irritant and corrosive and therefore has only a limited usefulness. The official preparation is *Chromium Trioxide* (*Chromic Anhydride, Chromic Acid*), U.S.P., B.P. It occurs as purplish-red crystals, freely soluble in water. Chromic trioxide should not be brought into intimate contact with organic substances, as serious explosions are likely to result. In therapeutics, the compound is employed in aqueous solution. In the strength of ten per cent it has been used for local application in the treatment of *Vincent's angina* but it is inferior to sodium perborate or organic arsenicals. A 20 per cent solution is sufficiently destructive to tissue to be employed for the removal of *warts.*

Chromate Poisoning. Poisoning by chromic acid or chromate salts is an industrial hazard encountered mainly in electrotyping, dyeing and plating industries. The main symptoms of industrial poisoning are due to the local actions of the chromate ion on the skin and upper respiratory passages. Local ulceration of the skin occurs, and if exposure continues the ulcers burrow deeply and are familiarly known as "chrome holes." The most common sites are on the hands, chiefly around the base of the nails, the knuckles and the forearms. Inhalation of the dust irritates the nasal mucosa and inflammation, ulceration and finally perforation of the nasal septum may occur. The oral ingestion of chromate compounds causes intense irritation of the gastro-intestinal tract resulting in vomiting and severe diarrhea which may become bloody. After absorption, the ion is toxic to capillaries and the kidney, and oliguria and circulatory shock are the prominent symptoms. *Treatment* consists in the oral administration of demulcents and the parenteral injection of large amounts of isotonic sodium chloride solution to protect the kidney in so far as is possible and to maintain the volume and composition of the extracellular fluids. Shock therapy should be instituted if indicated.

Sander and Camp (1939) reported an unusual case of chromium poisoning in an infant. The source of the chromium was a paint pigment. Symptoms were largely confined to the central nervous system and were not unlike those of lead encephalopathy.

Benzoic Acid. This compound has been widely used as a *food preservative.* In concentrations of 0.1 per cent it prevents bacterial growth if the medium in which it is acting is slightly acid. It is much less effective at an alkaline pH because benzoate salts are formed. Benzoic acid is relatively non-toxic and almost tasteless, and for this reason can be added to food. After ingestion, the benzoic acid is combined with glycine and excreted in the urine as hippuric acid. A daily intake of four to six grams leads to no toxic symptoms aside from slight gastric irritation. Larger doses have systemic effects not unlike those of the salicylates. A derivative of benzoic acid, *iodoxy-benzoic acid,* has been employed in the treatment of arthritis but is no longer favored.

Benzoic Acid, U.S.P., B.P., consists of colorless crystals readily soluble in organic solvents and soluble in water to the extent of 0.37 per cent. Benzoic acid can be safely applied to the skin in high concentrations. As one of the components of Whitfield's ointment it is extensively employed in the treatment of such conditions as *ringworm of the scalp, epidermophytosis,* etc.

Acetic Acid. This acid in five per cent concentration is bactericidal to many types of microorganisms. It is occasionally used in one per cent solution on the skin for surgical dressings. *Ps. pyocyaneus* is particularly susceptible to acetic acid. U.S.P. and B.P. preparations are *Glacial Acetic Acid* (99 per cent CH_3COOH), *Acetic Acid* (36 per cent CH_3COOH) and *Diluted Acetic Acid* (six per cent CH_3COOH).

Boric Acid. This is a very weak germicide and certain organisms such as *Staph. aureus* are not killed by long exposure to a saturated aqueous solution. However, aqueous solutions are effective in inhibiting bacterial growth. The non-irritating properties of such solutions make them suitable for applications to delicate structures such as the cornea of the eye. Although it is not very toxic, serious poisoning can result from the ingestion of five grams of boric acid. Symptoms include nausea, vomiting, abdominal pain, diarrhea, headache, visual disturbances, weakness, restlessness, renal injury, collapse and occasionally death. Treatment is purely symptomatic. Chronic use of boric acid may result in eczema, localized edema, stomatitis and a gray line on the gums.

Preparations and Uses. Boric Acid, U.S.P., B.P., is a colorless, odorless compound. It is soluble to the extent of approximately five per cent in water and 25 per cent in glycerin. It is commonly employed as *Boric Acid Ointment,* U.S.P., B.P. (10 per cent boric acid), *Glycerite of Boroglycerin,* U.S.P., B.P. (31 per cent boric acid in glycerin), and the saturated aqueous solution. Boric acid is also employed as a dusting powder diluted to the extent desired with some inert material. The above preparations are used in certain skin and mucosal lesions such as *eczema, erysipelas, impetigo, burns, epidermophytoses, bed sores,* etc. Boric acid solutions are also employed as a *mouth wash* and for *irrigation of the bladder.*

Salicylic Acid. This acid is a weak germicide and fungicide. Its local actions have been discussed under the salicylates.

Mandelic Acid

Mandelic acid is an effective urinary antiseptic. Prior to its introduction into therapy it was known that a highly acid urine was bactericidal and the clinical procedure employed to lower urinary pH for the control of urinary infections was to administer acid-forming salts or to prescribe a ketogenic diet. Fuller (1933) demonstrated that beta-hydroxybutyric acid, which is excreted in the urine, was the active bactericidal agent. The ketogenic diet is cumbersome and unpleasant, but it is the only means by which the urinary excretion of beta-hydroxybutyric acid can be assured for when this acid is given by mouth it is metabolized. Rosenheim (1935) undertook a study of a number of related keto and hydroxy acids and observed that mandelic acid, after oral administration, was excreted as such in the urine and that in an acid medium it was bactericidal. He therefore introduced it as a urinary antiseptic. Mandelic acid therapy in urinary infection has been reviewed by Braasch (1937) and by Rosenheim (1938).

Factors Influencing the Bactericidal Action of Mandelic Acid. Aside from the variation in the susceptibility of particular microorganisms, the two factors which largely determine the bactericidal effect of mandelic acid are its concentration and the pH of the medium in which it is acting. Helmholtz and Osterberg (1936) have shown that for equal bactericidal activity against the majority of organisms, the following relationship between concentration of mandelic acid and urinary pH is necessary: one per cent solution at pH 5.7, 0.5 per cent solution at pH 5.3, and 0.25 per cent solution at pH 5.0. In clinical practice the therapeutic objective is to keep the pH of the urine below 5.5 (red to methyl red indicator) and the concentration of mandelic acid above 0.5 per cent (Figure 86).

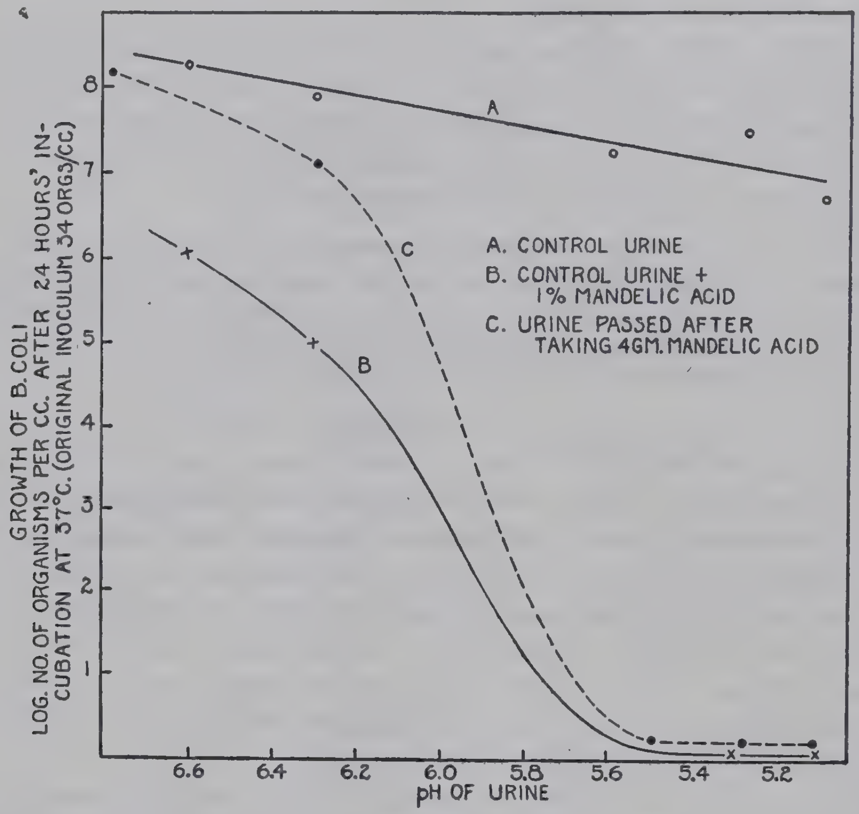
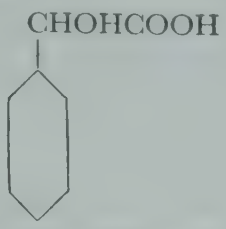


FIGURE 86. *Bactericidal action of urine with and without mandelic acid.*

Observe that the control urine does not become bactericidal even at a low pH. When mandelic acid is added to the control urine an increase in bactericidal potency occurs, but this is not significant until high acidities are obtained. The same phenomenon is observed in urine passed after the ingestion of four grams of mandelic acid. (After Rosenheim, 1937. Courtesy of the *Proceedings of the Royal Society of Medicine.*)

Chemistry and Preparations. Mandelic acid has the following structural formula:



Mandelic Acid

It is the simplest of aromatic hydroxy acids. Schotten (1883) was the first to show that this substance was not oxidized in the body but rather was excreted unchanged in the urine and Knoop (1904) made use of this fact in support of his well-known theory of the beta oxidation of fatty acids.

Mandelic Acid, U.S.P., consists of white crystals which are soluble in water. In therapy, the salts of mandelic acid are commonly employed. The sodium, ammonium and calcium salts are available. When sodium mandelate is prescribed it should be accompanied by an acidifying agent in order to assure a proper urinary pH. The ammonium and calcium salts are in themselves acidifying for the ammonium cation is converted to urea and the calcium cation is excreted into the intestine or deposited in bone. The ammonium salt is highly hygroscopic and is therefore usually dispensed as a syrup or elixir. Calcium mandelate is non-hygroscopic, almost tasteless and thus is very conveniently administered in tablet form.

Dosage and Methods of Administration. Inasmuch as mandelic acid is completely eliminated by the kidney within a 24-hour period, the dose is adjusted so that the total amount administered in a day divided by the 24-hour urinary volume permits a concentration of drug between 0.5 and 1.0 per cent. The usual dose is three grams administered four times daily. The fluid intake is limited to one liter in order that the total urinary volume approximates 1200 cc. In the event that sodium mandelate is employed, four grams of ammonium chloride or ammonium nitrate should also be administered daily in divided doses. It is usual to continue therapy for from 10 to 12 days. If by this time the urine is not sterile the drug should be withdrawn and resumed only after an interval of 10 to 14 days. This rest period prevents the bacteria from becoming resistant to mandelic acid and also lessens the danger of renal injury. The drug should be given after meals to prevent gastric irritation and nausea. Children tolerate mandelic acid very well and the doses recommended by Newns and Wilson (1936) are as follows:

Up to 6 months	2 grams daily
6 months to 2 years	2 to 4 grams daily
2 to 5 years	4 to 6 grams daily
5 to 12 years	6 to 8 grams daily

Bactericidal Properties. Mandelic acid is germicidal for *E. coli, Aerobacter aerogenes, Pseudomonas, Alcaligenes, Salmonella* and *Shigella. Streptococcus faecalis* and *staphylococcal* infections are more resistant to this agent, especially when the infection is encountered in adults. However, persistent therapy will often render the urine sterile. Cases of *paratyphoid* urinary infection, cured by mandelic acid, have also been reported. Infections caused by organisms which split urea to ammonia as, for example, certain genera of *Proteus* and *B. pyocyaneus,* will not respond to mandelic acid treatment inasmuch as it is not possible to make the urine sufficiently acid.

Indications and Contraindications. Approximately 80 to 90 per cent of uncomplicated urinary infections respond to mandelic acid. The primary indication for mandelic acid is acute or chronic urinary tract infections due to organisms susceptible to the bactericidal action of the drug. Benefit is usually obtained even if the infection is not entirely eliminated. The drug is also useful if employed preliminary to instrumentation of or operation on the urinary tract. It is also used postoperatively to prevent infection.

The primary contraindication to the use of mandelic acid is impaired kidney function. If the drug is not efficiently excreted, a severe acidosis and renal damage may result. In elderly individuals, in patients with only one kidney, in those with chronic bilateral renal disease or in individuals with albumin, red blood cells or casts in the urine, it is best to ascertain the level of renal function before administering the drug. Poor renal function dictates caution. Other patients to whom mandelic acid must be given with care include those with severe organic heart disease, diabetes mellitus, marked debilitation and gout.

Causes for Failure. Failure to sterilize the urinary tract may be due to improper urinary pH. In such an event the dose of acidifying salt may be too low, there may be ammonia-forming bacteria present, or renal function may be impaired to such a degree that it is impossible to obtain an acid urine. In the last-mentioned circumstance it is dangerous to administer acidifying salts because uncompensated acidosis or further renal injury may result. The presence of urinary stasis due to strictures, tumors, foreign bodies, urinary lithiasis, etc., markedly impairs the efficacy of the drug.

Untoward Reactions. Mandelic acid rarely causes serious reactions if the contraindications listed are respected. Nausea is the most frequent untoward effect but usually disappears spontaneously after a few days. It occurs with all preparations and can be lessened by taking the drug with meals and building up the dose gradually during the first few days of therapy. Diarrhea also may occur, but is infrequent. Microscopic hematuria can be observed in one to two per cent of cases. It ceases after the drug is withdrawn and does not necessarily accompany a second course of treatment. Occasionally hyaline casts may be observed. Mild systemic reactions which have been classified as idiosyncrasy to mandelic acid have been reported. They consist of ringing in the ears, slight deafness, muscular pains and cutaneous lesions, especially urticaria. These untoward effects are rarely seen and disappear as soon as the drug is withdrawn.

In experimental studies on the toxicity of mandelic acid in animals, Carroll, Lewis and Kappel (1938) noted that large doses of the drug were likely to cause liver damage characterized by focal necrosis. They did not regard this as a serious contraindication to the clinical use of the drug but believe that mandelic acid should be employed cautiously in patients with liver damage.

HALOGEN AND HALOGEN-CONTAINING COMPOUNDS

Iodine

Iodine is one of the oldest of the antiseptics, the history of its use as a germicide dating back to 1873. Despite the present wide choice of antiseptics, iodine is still extensively employed, the drug having survived on the basis of efficiency and economy.

Germicidal Action. Although many studies have been made on the germicidal action of iodine, the exact mechanism by which the element is toxic to microorganisms cannot be stated. In the absence of organic matter, iodine exerts a germicidal effect in such low concentration that it is not likely that the drug acts as a protein precipitant. Its mechanism of action is probably similar to that of chlorine, namely to iodize and oxidize the chemically active elements of bacterial protoplasm. Only free iodine is germicidal, the salts of the element being inactive in this regard.

Iodine is an effective agent against all bacteria and is unique in that it shows little selective action, the concentration of iodine necessary to disinfect being practically the same for all microorganisms. Gershenfeld and Miller (1932) found that the phenol coefficient of iodine for most bacteria averaged approximately 2.0 for each one per cent of iodine present. In other words the phenol coefficient of elemental iodine is approximately 200.

Tissue Toxicity. The value of iodine as an antiseptic is emphasized by the studies of Salle and coworkers (1935, 1937, 1938). These investigators have devised a method for the testing of germicides in which the toxicity for tissue of the agent being considered is weighed against bactericidal potency. Toxicity is determined by the effect on the growth of embryonic tissue. Using this therapeutic index, Salle and associates found iodine to be superior to any other antiseptic studied. A similar conclusion was drawn by Nye (1937) who employed leukocytes to measure tissue toxicity.

Fungicidal Action. Iodine is an effective fungicide, a fact that is often overlooked in the treatment of fungicidal infections. Schamberg, Brown and Harkins (1931) found that *Epidermophyton inguinale* was killed by exposure for 15 minutes to a 1:85,000 solution of iodine. Emmons (1933), in a comparison of various fungicidal agents with phenol, found iodine to be highly effective and assigned to the element a phenol coefficient of 3000 against *Trichophyton gypseum* and *Monilia albicans.* Iodine is also a potent amebicide and is moderately viricidal.

Preparations. *Iodine,* U.S.P., B.P., consists of grayish-black brittle plates with a metallic luster and characteristic odor. The element is traditionally used as an antiseptic in the form of its tincture. There are two official tinctures in the U.S.P. *Tincture of Iodine,* U.S.P., contains seven per cent iodine and five per cent potassium iodide in alcohol (alcoholic content 83 per cent). *Mild Tincture of Iodine,* U.S.P., contains two per cent iodine and 2.3 per cent sodium iodide in *diluted* alcohol (alcoholic content 46 per cent). *Strong Solution of Iodine,* B.P., and *Weak Solution of Iodine,* B.P., contain 10 per cent and 2.5 per cent elemental iodine and 6.0 per cent and 1.5 per cent potassium iodide, respectively. Their alcoholic content is approximately 80 per cent. *Simple Solution of Iodine,* B.P., is merely 9.0 per cent iodine in 95 per cent alcohol.

A fact often overlooked is that iodine is highly germicidal in aqueous solution. Iodine dissolves readily in water in the presence of an iodide salt. The official aqueous solution of iodine is *Compound Solution of Iodine* (*Lugol's Solution*), U.S.P. (*Aqueous Solution of Iodine,* B. P.). It contains five per cent of free iodine, and Nye (1937) has shown that even a 1:6.4 dilution of this official solution is more active *in vitro* than the majority of commercial germicides. *Iodine Ointment,* U.S.P., contains four per cent of iodine in wool fat, wax and petrolatum but the element loses much of its effectiveness when employed in this form. The so-called "colorless tincture of iodine" is officially known as *Tincture of Iodides,* N.F. In this preparation, iodine in potassium iodide is decolorized with ammonium hydroxide and alcohol is added so that the final alcoholic content is approximately 45 per cent. The iodine probably is converted to NH_4OI, a compound which can liberate free iodine. Thus some of the antiseptic action of free iodine is retained, but the preparation is unstable and inferior to solutions of elemental iodine. *Stronger Tincture of Iodine,* N.F., contains 16.5 per cent free iodine, an unnecessarily high concentration.

Iodine Poisoning. Elemental iodine is more toxic than the iodine salts, and tincture of iodine is often taken with suicidal intent. That iodine is highly toxic, however, is a popular fallacy, and although many cases of attempted suicide with tincture of iodine are recorded annually, few patients succumb to the effects of the drug. Moore (1938) analyzed the cases of attempted suicide treated at the Boston City Hospital between 1915 and 1936. Of 1195 cases, 327 individuals ingested iodine in some form, yet from this large group no death was recorded. However, the impression must not be gained that iodine is non-toxic for Finkelstein and Jacobi (1937) report 18 fatal cases of iodine poisoning from a study of the records of the Medical Examiner's Office of New York City for the six years previous to their publication. In nine of the cases the amount ingested varied between one and eight ounces of the tincture.

The toxic effects of iodine are largely due to the corrosive effects of the element in the gastro-intestinal tract. Iodine is highly corrosive and on this basis the number of deaths from ingestion of iodine would be high were it not for the fact that the element is very reactive. Thus iodine combines with the starches, proteins and fats in the digestive tract and in this manner is inactivated. Little free iodine is absorbed from the intestinal tract, but rather it reaches the blood stream in the form of iodides. It is probable that the pathological changes which have been recorded in the fatal cases of iodine poisoning and attributed to the systemic effects of iodine are largely the result of shock and tissue anoxia.

Symptoms. The symptoms of iodine poisoning arise chiefly from the gastro-intestinal tract. The diagnosis is facilitated by the fact that the oral mucous membranes are stained brown. Reflex vomiting usually occurs, and if starch is present in the stomach the vomitus is colored blue. The local actions of iodine lead to gastro-enteritis, abdominal pain and diarrhea which may be bloody. Large amounts of fluid are lost by vomiting and diarrhea, and shock may result from anhydremia and tissue trauma. In fatal cases, death usually occurs in from one to 48 hours. The cause of death may be circulatory collapse due to shock, acute corrosive gastritis, asphyxiation from edema of the glottis, aspiration pneumonia, etc. In rare instances, delayed death from stenosis of the esophagus has been recorded.

Treatment. Efficient chemical antidotes are available for the treatment of iodine poisoning. Gastric lavage with a solution of soluble starch can readily remove all the iodine present in the stomach. Alternative antidotes are sodium thiosulfate (five per cent solution) or protein. The stomach should be lavaged until all traces of iodine are removed. Further treatment consists in replenishing the fluids and electrolytes lost from the intestinal tract. The intravenous administration of copious amounts of isotonic sodium chloride solution is indicated. Shock therapy should be instituted if necessary.

Idiosyncrasy. In rare instances, an individual may exhibit an idiosyncrasy to iodine and react severely even to moderate amounts of iodine applied to the skin. Symptoms usually take the form of severe constitutional reactions with fever and a generalized skin eruption of almost any type. Seymour (1937) reviewed 15 cases of iodine sensitivity and reports one of his own experience in which the patient died of exfoliative dermatitis following the application of iodine to the skin prior to pneumothorax.

Therapeutic Uses. The chief use of solutions of elemental iodine is in the *disinfection of the skin.* In this regard iodine is probably superior to any other agent, although it is probable that no germicide is effective in rendering the skin sterile. As a skin antiseptic, iodine is best employed in the form of the tincture, for the alcoholic vehicle facilitates spreading and penetration. If full-strength tinctures are employed, the excess iodine should be removed with alcohol or vesication and desquamation may occur. Iodine may also be employed in the *treatment of wounds and abrasions.* If iodine is to be applied to abraded tissue, aqueous solutions are less irritating than the tincture. Nye (1937) recommends the use of 0.5 or 1.0 per cent aqueous solution of iodine in iodide for wounds and abrasions and a 0.1 per cent solution for irrigations. These concentrations can readily be made by proper dilution with water of the *Compound Solution of Iodine,* U.S.P. For application to *mucous membranes,* a two per cent solution of iodine in glycerin is the preparation of choice. In the treatment of *skin infections* due to bacteria and fungi, mild tincture of iodine or compound solution of iodine diluted to half strength with water may be employed.

Elemental iodine is not employed as an *amebicide,* but organic iodides are widely used for this purpose (page 934). However, in an emergency, if it is feared that drinking water is infested with pathogenic ameba, the addition of one drop of tincture of iodine to each quart of water will kill not only ameba but also bacteria within fifteen minutes without rendering the water unpalatable.

Iodine is an alkaloidal precipitant, and inasmuch as it is usually available it is often employed as a *chemical antidote* in the treatment of poisoning by alkaloids. For this purpose, tincture of iodine is diluted 1:250, administered by stomach tube and subsequently removed by gastric lavage.

Iodoform

Iodoform (CHI_3), U.S.P., B.P., is a lemon-yellow powder with a characteristic disagreeable and persistent odor. The compound is practically insoluble in water and it is difficult to estimate its bactericidal potency. An aqueous suspension of the drug is not germicidal and is only slightly antiseptic. When applied to tissues, the compound slowly releases elemental iodine, and this is the basis for its mild antibacterial action. Iodoform was formerly used rather extensively for the dressing of wounds, but is rather ineffective and is now seldom employed.

Chlorine-containing Compounds

The ability of chlorine to arrest putrefaction and destroy accompanying odors was recognized and employed long before the concept of microorganisms had originated. The first wide use of chlorine as an antiseptic was in connection with the sterilization of water supplies, a practice which spread rapidly during the first decade of the twentieth century. It was not until the World War of 1914–1918, however, that chlorine-containing compounds were extensively employed in medicine and surgery. The investigations of Dakin (1916, *et seq.*) and the introduction of the solution bearing his name for the treatment of surgical wounds marked the beginning of the extensive use of chlorine antiseptics.

The chlorine-containing antiseptics are active by virtue of the fact that they liberate free chlorine. In the following discussion, therefore, the germicidal actions of chlorine will first be considered, after which the distinguishing features of the individual compounds which release chlorine will be presented. The toxicology of chlorine gas has been discussed elsewhere.

Mechanism of Germicidal Action. The oldest theory as to the mechanism of germicidal action of chlorine is that the element reacts with water to liberate nascent oxygen and thus destroys bacteria by oxidation. The chemical reaction may be depicted as follows:

$$Cl_2 + H_2O \rightarrow 2HCl + O$$

The theory is insufficient, however, completely to account for the bactericidal actions of the element for the reasons that oxygen from other sources does not kill microorganisms as readily as does chlorine and also that chlorine is known to exert a bactericidal action under conditions in which the direct oxidation of bacterial cells is precluded (McCulloch, 1936). It has therefore been suggested that the element directly chlorinates the protein of bacterial protoplasm, probably reacting with the hydrogen of the amino groups to form chloramines, as follows:

$$R-CO-NH-R + Cl \rightarrow R-CO-NCl-R + H$$

Germicidal Efficiency. Elemental chlorine is one of the most potent of germicidal agents. The concentration of chlorine necessary to kill most organisms in from 15 to 30 seconds varies between 0.10 to 0.25 parts per million. On the basis of pure chlorine, the phenol coefficient of the element for different bacteria varies between 150 and 300. However, acid-fast organisms are uniquely resistant to chlorine, 500 times the concentrations cited being necessary to destroy *Mycobacterium tuberculosis*. Chlorine is viricidal and amebicidal, as well as bactericidal.

The bactericidal activity of chlorine can be influenced by a number of factors. Chief of these is the presence of organic matter. Chlorine is a highly reactive element and thus can be bound by organic material. In the disinfection of inanimate objects, as for example water, the uptake of chlorine by the extraneous organic matter present is known as the *chlorine demand*. Comparatively little chlorine is needed to disinfect materials which have a slight chlorine demand. In the presence of excessive organic matter, chlorine is not the disinfectant of choice. As an example of the influence of organic matter on the bactericidal action of chlorine may be cited the problem encountered in the purification of water. It is generally considered that a residual chlorine content of 0.2 to 0.4 parts per million of water affords a generous margin of safety. In order to attain this concentration of chlorine in relatively pure water, it is necessary to add only 0.5 parts of chlorine per million, whereas in grossly polluted waters 20 parts per million are scarcely sufficient.

Other factors which influence the bactericidal action of chlorine are pH and temperature. Chlorine is more antiseptic in acid than in alkaline solutions. Also compounds which liberate chlorine do so more readily in an acid medium. In acid solution, chlorine forms hypochlorous acid (HOCl), a compound which readily yields free chlorine. In alkaline solution, much more stable chlorine compounds are formed. At pH 9.0, less than 20 per cent of available chlorine in solution is present as hypochlorous acid whereas at pH 6.0 all the available chlorine is in this form. The bactericidal action of chlorine is 10 times greater at pH 6.0 than at pH 9.0. The temperature coefficient of chlorine is relatively low. However, it can be demonstrated that the element is more rapidly bactericidal at high than at low temperatures.

Chlorine-containing Compounds. Chlorine itself has a limited usefulness as an antiseptic due to the difficulties in handling the element in its gaseous state, and chlorine water is very unstable. There are a number of compounds, however, which slowly yield elemental chlorine and these can be employed for the disinfection of inanimate objects and in surgery. The germicidal efficiency of such compounds is related to the ease and extent of the liberation of chlorine. The chlorine which can be so released is known as "available chlorine." The amount of available chlorine of a compound cannot be calculated but rather must be determined by chemical test. The method employed depends upon the liberation of free iodine from potassium iodide by elemental chlorine. The details for the procedure are given in the U.S.P. and B.P.

Hypochlorite Solutions

There are a number of solutions which liberate chlorine from hypochlorites. They are known under various names such as Dakin's solution, Dakin-Carrel solution, Labarraque's solution, etc. *Solution of Sodium Hypochlorite,* U.S.P., is the official preparation of this type. It contains five per cent of NaOCl. This concentration is too high to be employed on tissues and for surgical purposes *Diluted Solution of Sodium Hypochlorite* (*Modified Dakin's Solution*), U.S.P., is employed. This preparation contains approximately 0.5 gram of NaOCl and 0.45 gram of available Cl per 100 cc. The pH of the solution is adjusted with sodium bicarbonate using phenolphthalein as the indicator. A solution of comparable strength is *Surgical Solution of Chlorinated Soda* (*Dakin's Solution*), B.P.

Solutions of sodium hypochlorite are relatively unstable and should be freshly prepared. They are employed in the treatment of *suppurating wounds* and are not only germicidal but also dissolve necrotic tissue. A disadvantage of the hypochlorites is that they dissolve blood clots and delay clotting through interference with thrombin. Chlorine antiseptics are also somewhat irritating to the skin. The diluted solution is employed in full strength, and is often administered by continuous irrigation (Carrel technic). Diluted solution of sodium hypochlorite is also widely employed as a foot-bath for the prophylaxis of *epidermophytosis.*

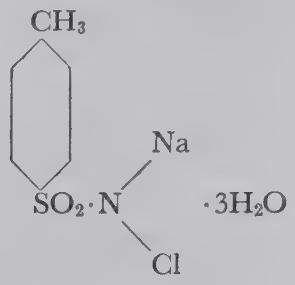
Chlorinated Lime

Chlorinated Lime, B.P., is too irritating to be used on tissues, but is widely employed for the *disinfection* of inanimate objects and drinking water. The compound is also the basis for the preparation of solutions of sodium hypochlorite. Chemically it consists of a mixture of calcium chloride and calcium hypochlorite and should contain a minimum of 30 per cent available chlorine. Chlorinated lime is relatively unstable and loses much of its activity, even with careful storage, over a period of a year.

Chloramines

The chloramines used as medicinal agents are compounds in which chlorine is linked to nitrogen in the form of available chlorine. The compounds were synthesized long before they were introduced into medicine by Dakin and his coworkers (1916).

Chloramine-T. *Chloramine-T* (*Chloramine*), U.S.P., B.P., is a white or faintly yellow crystalline powder having a faint odor of chlorine and soluble 1:7 in water. It has the following structural formula:

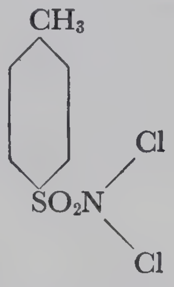


Chloramine-T

Chloramine-T contains approximately 13 per cent chlorine, all of which is present in an available form. On exposure to air it decomposes slowly to yield chlorine. In solution, chlorine is released more rapidly but not as rapidly as from hypochlorites. Therefore chloramine solutions are less active germicides than sodium hypochlorite solutions possessing the same percentage of available chlorine. Also chloramine-T has less solvent action on necrotic tissue. On the other hand, chloramine-T has a longer duration of action, and is not rendered ineffective as rapidly by organic matter.

Chloramine is employed in one or two per cent solution for the irrigation and dressing of *wounds* and in 0.1 to 0.2 per cent solution for application to *mucous membranes.*

Dichloramine-T. *Dichloramine-T,* U.S.P., is a yellowish crystalline powder which is almost insoluble in water but readily soluble in organic solvents. It has the following structural formula:

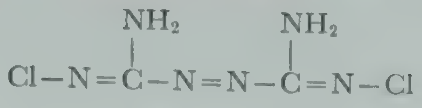


Dichloramine-T

Dichloramine-T contains approximately 30 per cent chlorine, all of which is present in an available form. It gradually decomposes on exposure to air losing chlorine.

Dichloramine-T is employed medicinally in the form of oily solutions. It is usually dissolved in *Chlorinated Paraffin* (*Chlorcosane*), U.S.P. Chlorinated paraffin consists of a liquid paraffin which has been treated with chlorine to the point of chlorine saturation. This chlorine is not available chlorine, and thus the preparation is not useful as a germicide. However, if dichloramine-T is dissolved in such a vehicle, none of the chlorine released from the chloramine is lost to the paraffin and all is available for therapeutic action. Solutions of dichloramine-T are more irritant, more solvent and more lasting than those of chloramine. A one or two per cent solution in chlorinated paraffin is employed for application to *mucous membranes,* and a five per cent solution is used for the dressing of *wounds.*

Azochloramid. *Azochloramid,* N.N.R., is a yellow crystalline compound, slightly soluble in water and glycerin, and has the following chemical structure:

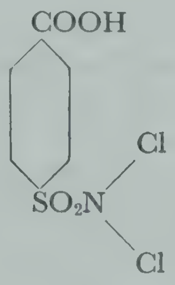


$$\mathrm{Cl-N=\overset{\displaystyle NH_2}{\overset{|}{C}}-N=N-\overset{\displaystyle NH_2}{\overset{|}{C}}=N-Cl}$$

Azochloramid

Its actions and therapeutic uses are the same as those of chloramine-T and dichloramine-T. However, it is claimed that the compound has a higher bactericidal activity in the presence of organic matter. Azochloramid is marketed in vials containing the drug and a mixture of salts. The contents of the vial when dissolved in a given volume of water form a germicidal buffered saline solution. In the treatment of *wounds*, a 1:1600 to 1:3300 solution is employed. The drug is also marketed as a 1:500 solution in triacetin.

Halazone. *Halazone*, N.N.R., is a chloramine having the following chemical structure:



Halazone

The drug is employed for the *sterilization of drinking water*, a concentration of 1:300,000 being lethal to the typhoid bacillus within two minutes. The drug is marketed in tablets containing sufficient halazone to sterilize one liter of water, and is of convenience for campers and individuals who do not have safe water available.

OXIDIZING ANTISEPTICS

A number of antiseptic drugs are toxic to microorganisms by virtue of the fact that they are oxidizing agents. The members of this group may be divided into two major divisions: those which release nascent oxygen and those which oxidize by other mechanisms. The important members of the first group are hydrogen peroxide, metallic peroxides, sodium perborate, and the permanganates. In the second group are the halogens (chlorine and iodine) and their active derivatives.

Compounds Releasing Nascent Oxygen

Molecular oxygen exerts a germicidal action by oxidizing constituents of the protoplasm of bacteria. Also anaerobic microorganisms are adversely affected by a high concentration of oxygen in their environment and compounds releasing oxygen have a bacteriostatic effect on bacteria of this type. Different species of microorganisms vary greatly in their sensitivity to oxygen. In general, it can be stated that the Gram-positive bacteria, certain spirochetes and trypanosomes are the most susceptible.

Although all compounds which release oxygen have the same basic mechanism of germicidal action, their individual properties differ considerably and are influenced by the ease with which oxygen is liberated, the actions of the cation linked with the oxygen-containing anion and the effects of the residual substance remaining after oxygen has been released. For this reason they require individual discussion.

Hydrogen Peroxide. Hydrogen peroxide is a very unstable compound which breaks down readily to form molecular oxygen and water. Medicinally, it is employed in the form of stabilized solutions. The official preparation is *Solution of Hydrogen Peroxide,* U.S.P., B.P., which contains three per cent hydrogen peroxide in water. It is a colorless, odorless liquid.

Hydrogen peroxide is an active germicide only as long as it releases oxygen. When applied to tissue, this action is of brief duration. Furthermore, solutions of hydrogen peroxide have poor penetrability and are relatively feeble germicides. For example, Dittmar and associates (1930) assign to commercial solutions of hydrogen peroxide a phenol coefficient of 0.012 against *Staph. aureus* and 0.014 against *E. coli.*

The most extensive use of hydrogen peroxide is in the *cleansing of wounds.* The effervescence of oxygen affords a mechanical means for the removal of tissue débris from inaccessible regions. Full or half strength solutions may be employed. The drug is also highly effective in the treatment of *Vincent's stomatitis* (Farrell and McNichols, 1937). For this purpose undiluted solution of hydrogen peroxide should be used as a mouth wash at least four times daily. The continued use of hydrogen peroxide as a mouth wash, even in half strength, may cause hypertrophied filiform papillae of the tongue ("hairy tongue"), but these disappear after the drug is discontinued (Miller and coworkers, 1938). Hydrogen peroxide has also been found of value in the treatment of *balanitis* (continuous irrigation with a two per cent solution) and of *Trichomonas vaginalis vaginitis.*

Metallic Peroxides. The metallic peroxides employed medicinally include sodium peroxide, calcium peroxide and zinc peroxide.

Sodium Peroxide, N.N.R., is a white, water-soluble, amorphous compound. In solution, it readily releases oxygen, leaving a residue of sodium oxide. The latter compound is strongly basic, and thus sodium peroxide has a limited usefulness as a therapeutic agent. It has been employed by dermatologists in the treatment of *acne* and the removal of *comedones.*

Calcium Peroxide, N.N.R., is a cream-colored, water-soluble powder containing not less than 60 per cent calcium peroxide. In contact with moisture it slowly releases oxygen. The compound is seldom employed, but in the past it was taken internally as an antacid and antiferment. Culmer, Atkinson and Ivy (1937) studied the actions of peroxides in the stomach for the purpose of ascertaining their clinical value as gastric antacids. Using gastric pouch dogs and human beings as subjects, they found that hydrogen peroxide was effective in decreasing gastric secretion. However, the action of the compound was unpredictable and caused discomfort, and in general peroxides were found unsuitable as antacid drugs.

Zinc peroxide is another metallic peroxide which slowly releases nascent oxygen, leaving a residue of zinc oxide. The latter exerts a slight astringent action. Zinc peroxide has been extensively investigated by Meleney and coworkers (1937, 1938). Meleney found it of value in the treatment of *oral infections* from anaerobic microorganisms. For this purpose, the powder is suspended in four parts of water and used as a wash. A 40 per cent suspension of zinc peroxide was also found to be highly effective in the disinfection, deodorization and healing of *wounds infected with anaerobes, microaerophiles* and certain aerobes including *hemolytic streptococci.* There is no official or N.N.R. preparation of zinc peroxide and it is difficult to obtain a uniformly active product.

Sodium Perborate. *Sodium Perborate,* U.S.P. ($NaBO_3 \cdot 4H_2O$), is a white, crystalline powder which releases nascent oxygen upon contact with moisture. Official preparations contain not less than nine per cent of available oxygen. Sodium perborate has been widely employed as an antiseptic for the oral cavity. After the release of oxygen, the residue is mildly alkaline, and this is supposedly advantageous. For use as a *mouth wash* it is usually employed as a two per cent solution and the compound is often incorporated in dentifrices. Miller and coworkers (1938) studied the effects of the continued use of sodium perborate as a mouth wash and dentifrice in a group of medical students. Twenty-one per cent of the group developed hypertrophied filiform papillae of the tongue but the lesions disappeared when the medication was discontinued. Continued application of the compound to the tongue and cheeks of experimental animals resulted in no pathological changes. The chief clinical use of sodium perborate is in the treatment of *Vincent's infection.* The compound is applied in the form of a paste made with water or glycerol. This is left in the mouth for five minutes and then rinsed out with warm water. Therapy can be supplemented by the use of a two per cent solution as a mouth wash. Excellent results have been reported from this technic.

There is no unanimity of opinion as to the dangers in the use of sodium perborate. Some investigators feel that the compound should only be used under close supervision, whereas others express the view that sodium perborate is an excellent and safe agent for oral hygiene for lay distribution.

Permanganates. The permanganates are probably the most valuable of the antiseptics which release nascent oxygen. There are two of clinical importance, potassium permanganate and zinc permanganate. The latter compound combines the actions of an oxidizing agent and an astringent.

Potassium Permanganate, U.S.P., B.P., consists of dark purple water-soluble crystals. Solutions are a deep purple and stain tissues or clothing. *Zinc Permanganate,* N.N.R., consists of dark brown crystals which are freely soluble in water. The compound releases oxygen more readily than the potassium salt and great care should be taken in bringing it in contact with easily oxidizable substances. If any foreign matter gains access to the bottle in which zinc permanganate is stored, oxygen is released and if the container is tightly stoppered an explosion may result. Persons have been injured in opening bottles of zinc permanganate.

Microorganisms vary greatly in their resistance to permanganates. For example, the concentration of potassium permanganate required to disinfect after exposure of an hour at room temperature varies for different organisms as follows: *Ps. pyocyaneus,* 15 parts per million; *E. coli,* 60 parts per million; *Staph. aureus* and *Proteus vulgaris,* 240 parts per million; *B. mesentericus,* 30 parts per thousand. The bactericidal efficiency of the permanganates is greatly reduced in the presence of organic matter. Concentrations stronger than 1:5000 are irritating to tissues.

Clinical Uses. The permanganates are employed clinically for a variety of purposes, but are used much less extensively than formerly. Their most extensive application is in the treatment of *urethritis,* and it is in this condition that zinc permanganate, because of its astringent action, is possibly preferable to the potassium salt. A concentration of 1:4000 is employed either as an injection or as a urethral douche. In the treatment of *gonorrhea,* potassium permanganate was at one time highly regarded and is still employed. The urethra is irrigated with solutions of increasing concentration, usually starting with 1:15,000 and ending with 1:8000. If an astringent action is desired, zinc permanganate can be substituted. Some urologists combine the use of permanganate and organic silver preparations. For irrigation of the bladder in the treatment of *persistent urinary infections,* a 1:5000 solution of potassium permanganate may be employed.

A one per cent solution of potassium permanganate has been used in the treatment of *Vincent's infections,* but if an oxidizing antiseptic is desired, hydrogen peroxide or sodium perborate is probably superior. The vesicular lesions of *epidermophytosis* have also been reported to respond to the application of one per cent solution of potassium permanganate. The compound is also useful in treating the vesicular stage of *eczema-dermatitis,* for which purpose a wet dressing of a 1:10,000 solution is employed.

The ability of potassium permanganate to oxidize organic substances finds other fields of usefulness besides the treatment of infections. *Venoms* can be destroyed by oxidation, and application of crystals of potassium permanganate to the site of a *snake bite* is of value provided the wound is opened widely and the circulation is stopped to prevent absorption. However, some take the view that the compound does more harm than good in that a crust is formed and this precludes the possibility of suction and drainage from the wound. A wet dressing of permanganate may be employed in the treatment of *ivy poisoning.* Permanganate solutions can oxidize many drugs, and gastric lavage with a concentration of 1:5000 is of some value as a *chemical antidote in poisoning.* Certain of the barbiturates, chloral hydrate, and many of the alkaloids are susceptible to oxidation in this manner. Alkaloids resistant to oxidation by permanganate are atropine and cocaine.

Potassium Chlorate. Potassium chlorate was introduced as an oxidizing germicide but the compound has little action against bacteria, retarding their growth barely more than do inert salts. In addition, the compound is likely to cause systemic poisoning. *Potassium Chlorate,* U.S.P., B.P., occurs as a white, crystalline powder which is soluble in water 1:16.5. Caution should be observed in handling the salt for when it is mixed with organic substances it may explode if heated or subjected to concussion. The drug, in from two to four per cent aqueous solution, has been used as a mouth wash in the treatment of *stomatitis.* A saturated solution has been employed for the local treatment of *Vincent's angina.* More effective and less toxic agents are available.

Chlorate Poisoning. The chlorate ion is not destroyed in the body, is excreted slowly by the kidney, and is thus capable of causing acute or subacute poisoning. The toxic dose of potassium chlorate has been placed at approximately five grams, but death has resulted from the ingestion of smaller amounts and recovery has followed the swallowing of much larger quantities. The continuous use of the salt may lead to a cumulative toxic effect. The chlorates exert a local irritant action in the gastro-intestinal tract and acute poisoning is usually marked by abdominal pain, nausea and vomiting. After absorption, the chlorate ion is toxic to blood, causing the destruction of red blood corpuscles and the conversion of hemoglobin to methemoglobin. The kidney is injured either by the drug itself or by the fragmented blood corpuscles and free hemoglobin. Death is caused by extensive methemoglobinemia or acute nephritis. The symptoms of poisoning are those which accompany methemoglobinemia, hemoglobinuria, anoxia and renal damage. *Treatment* includes the removal of the drug from the gastro-intestinal tract by gastric lavage and saline cathartics, combating anoxia by transfusion and by the use of small amounts of methylene blue to convert methemoglobin to hemoglobin (page 1032), the use of alkalis to prevent anuria (page 246) and symptomatic therapy. Cochrane and Smith (1940) have reviewed the literature on chlorate poisoning and report a fatal case which resulted from a pharmacist's error in dispensing potassium chlorate instead of potassium chloride. The patient ingested 30 grams over a three day period and died on the ninth day.

HEAVY METALS AND THEIR SALTS

Mercury Compounds

The inorganic mercury compounds were among the earliest antiseptics to be used, being introduced soon after phenol. Although they are still employed, it is now appreciated that their germicidal activity is much lower than was originally supposed. The compounds depend for their action on the release of the mercuric (Hg^{++}) ion which has an affinity for and a precipitant action on protein. This action is by no means selective for bacterial protoplasm and therefore inorganic mercury compounds are very irritant to tissue, have poor penetrability, and lose much of their germicidal potency in the presence of extraneous protein. Inorganic mercury preparations are also very toxic after absorption (page 733). Another disadvantage is that those inorganic compounds which ionize most completely corrode metal. Lastly, there is evidence that the action of mercury is reversible and concentrations of mercuric chloride which were originally considered to be bactericidal are only bacteriostatic, as can be demonstrated by the fact that removal of the mercury from a supposedly sterilized medium by precipitation of the mercuric ion permits the resumption of bacterial growth. Spores are also very resistant to the action of mercury compounds.

These obvious disadvantages of the inorganic mercury preparations led to the synthesis of complex organic mercury-containing compounds more suited for therapeutic application. Many valuable antiseptics have been obtained. The mechanism of action of the organic derivatives has not been explained. The simplest theory is that organic mercurials are likewise effective through the release of the mercuric ion; but this is difficult to reconcile with the fact that they are not as highly ionized as the inorganic salts, and yet are much more active. Furthermore, they have a specificity of action which could not be expected from a protein precipitant in that various organic mercurials show their maximum efficiency against different microorganisms. It must be pointed out, however, that mercuric chloride also has a selective action against certain microorganisms. Fildes (1940) presented evidence that mercury exerts a bactericidal action in much the same manner as arsenic exerts a treponemicidal action, namely, by combining with the sulfhydril groups in the bacterial cells and in this way interfering with cellular metabolism. This may explain the facts which are incompatible with the view that mercurial germicides are protein precipitants. A comparison of the bacteriostatic action of mercuric chloride and certain organic mercurials is presented in Table 44.

In addition to their greater bactericidal activity, the organic mercurials have a greater tissue penetrability, are less irritant and also less toxic than the inorganic salts.

Mercuric Chloride. This compound, the oldest of the mercury antiseptics, is used only as a disinfectant for inanimate substances or the unabraded skin. It is too irritating and toxic to apply to an abraded surface. It is often employed as a surgeon's hand wash in a concentration of 1:2000. It is also used for the sterilization of clothes, as for example diapers, in a dilution of 1:1000. A 1:1000 solution is employed for the sterilization of certain surgical instruments which are harmed by boiling. For getting rid of parasites such as the head louse or crab louse, solutions of mercuric chloride in 50 per cent alcohol are effective. For the scalp a 1:500 solution is employed and for the body a 1:1000 solution.

Mercuric Bichloride, U.S.P., B.P. (*Mercuric Chloride, Corrosive Sublimate, Corrosive Mercuric Chloride*), is usually dispensed in the form of official tablets, *Large Poison Tablets of Mercury Bichloride,* U.S.P., and *Small Poison Tablets of Mercury Bichloride,* U.S.P. The tablets contain 0.5 and 0.125 gram of mercuric chloride, respectively. They must be of irregular shape, of a distinctive color, and dispensed in containers of irregular shape bearing a "poison" label. By tradition, tablets of mercuric chloride are colored blue, and therefore if an acutely ill patient has a blue-stained vomitus, it is suggestive evidence of mercury poisoning.

Miscellaneous Mercuric Salts. There are a number of mercury salts which do not ionize to the extent of mercuric chloride. They are less irritating to tissue, do not corrode instruments and can be applied to mucous membranes. Several are even injected for their systemic effects as diuretics or in the treatment of syphilis. As diuretics they are inferior to and more dangerous than the organic mercurials (page 639) and as antisyphilitics they are not as effective as bismuth injections or mercury by inunction. These salts are also ill suited for application to tissue, being surpassed both with respect to germicidal efficiency and safety by a variety of other compounds. Therefore they are best regarded merely as substitutes for mercuric chloride. The following salts may be included in this group: *Mercuric Benzoate,* N.N.R., *Mercuric Cyanide,* N.N.R., *Mercuric Oxycyanide,* N.N.R., B.P. ($Hg(CN)_2 \cdot HgO$), *Mercuric Salicylate,* U.S.P., *Mercuric Succinimide,* U.S.P., *Red Mercuric Iodide,* N.F., B.P., and *Potassium Mercuric Iodide,* N.N.R.

Insoluble Mercury Compounds. The insoluble salts of mercury and metallic mercury are incorporated in ointment bases for use as *antiseptics.* When compounded in this manner, solution is slowly effected by the proteins and salts of the tissues, and the mercury ion in low concentration can thereby exert its action over long periods of time. *Yellow Mercuric Oxide,* U.S.P., B.P. (HgO), is a water-insoluble mercury salt. The official ointment of this salt contains a concentration of one per cent in wool fat and petrolatum and is known as *Yellow Mercuric Oxide Ointment,* U.S.P. It is commonly employed for application to the eye. It is also of value in *epidermophytosis, pruritus ani* and *louse infestation. Ammoniated Mercury,* U.S.P., B.P., an insoluble salt ($HgNH_2Cl$), is also used in ointment form. *Ammoniated Mercury Ointment,* U.S.P., contains a 10 per cent concentration of the salt in a base of wool fat, white wax and white petrolatum. The B.P. ointment contains five per cent of the salt. Ammoniated mercury ointment is chiefly used as a skin antiseptic and is especially effective in *impetigo contagiosa, ringworm* and certain other dermatoses. It is also used for scaling in *psoriasis,* in *pruritus ani* and in *pinworm* and *crab louse infestation. Strong Mercurial Ointment,* U.S.P., and *Mild Mercurial Ointment,* U.S.P., are preparations which consist of metallic mercury in a base of wool fat, white wax and petrolatum. The strong ointment contains 50 per cent and the mild 30 per cent of metallic mercury. *Ointment of Mercury,* B.P., contains 30 per cent mercury. Their chief use is in the treatment of *syphilis* but they also have been employed in *pediculosis.* Other official mercury ointments are *Strong and Dilute Ointments of Mercury Nitrate,* N.F. (7.0 per cent mercury), *Ointment of Mercurous Chloride* (*Calomel Ointment*), N.F. (30 per cent mercurous chloride; B.P., 20 per cent mercurous chloride), *Ointment of Red Mercuric Oxide,* N.F. (10 per cent mercuric oxide), *Compound Ointment of Mercury,* B.P. (12 per cent mercury) and *Ointment of Oleated Mercury,* B.P. (25 per cent oleated mercury).

Organic Mercurial Antiseptics. The organic mercurials are compounds in which mercury is present in complex organic combination. As a group they are more bactericidal, less irritating and less toxic than the inorganic mercurial salts.

Mercurochrome, N.N.R. This compound was the first of the organic mercurial antiseptics to be introduced. Despite evidence to the contrary, it is still considered by many as being a highly active germicide. Actually, as can be seen from Table 44, it is only feebly active and must be regarded rather as a bacteriostatic agent than as a bactericide. Chemically, mercurochrome is a fluorescein derivative (dibromhydroxymercurifluorescein). It is prepared as the disodium salt and in this form is soluble in both alcohol and water. The compound is a dye and in solution has a brilliant red color. Tissues are deeply stained red by mercurochrome solutions and the psychological effect of this staining property is such that the laity attribute an antibacterial potency to mercurochrome which it does not possess.

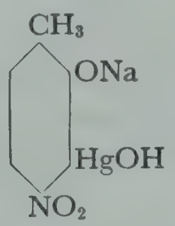
Mercurochrome is non-irritating to tissue. On the other hand, the dye has poor penetrability for living tissue (von Oettingen and coworkers, 1932) and its bactericidal activity is greatly reduced by organic matter and markedly affected by hydrogen-ion concentration. For example, at the pH of the body fluids, mercurochrome is relatively impotent; it is a relatively poor skin disinfectant (Simmons, 1928); and it is not reliable as a surface antiseptic for mucous membranes (Rodriguez, 1928).

Mercurochrome has been injected intravenously for the control of septicemia. Injections may be accompanied by alarming reactions characterized by a high temperature and vomiting and sometimes by severe diarrhea and prostration. Systemic mercury poisoning is also likely to follow. The clinical results obtained have not been promising.

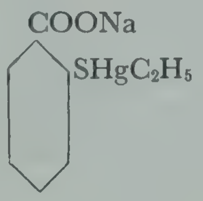
Mercurochrome has been widely employed. The many therapeutic applications include the use of this compound against all types of genito-urinary infections and for disinfection of the skin, mucous membranes and wounds. Although mercurochrome may be of limited value, for each of its many uses there is probably available a much more effective compound.

Mercurochrome is marketed in the following forms: two per cent aqueous solution, two per cent solution in alcohol and acetone, powder, tablets, suppositories, applicator sticks, and in sterile ampules for parenteral administration.

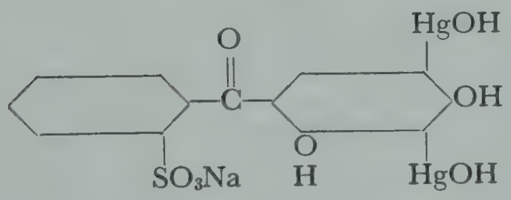
Metaphen, N.N.R., *Merthiolate,* N.N.R., *Meroxyl,* N.N.R. and *Merphenyl Nitrate.* These organic mercurial antiseptics have many features in common and thus can be conveniently discussed together. Their chemical constitution is indicated in the following structural formulas:



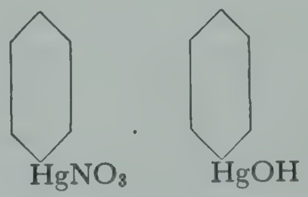
Metaphen
(Sodium Salt)



Merthiolate



Meroxyl



Merphenyl Nitrate

Many discordant results as to the antiseptic action of this group of organic mercurials have appeared in the literature. However, most investigators are agreed that the compounds are more active and less irritating than the simpler mercury salts. The comparative bactericidal activity of the various mercurial antiseptics as obtained by one investigator is presented in Table 44. It should be emphasized, however, that the organic mercurials are relatively ineffective in killing spores and are not as efficient as is commonly believed for disinfecting instruments (Brewer, 1939).

The organic mercurials can be employed as substitutes for the more highly ionized type of mercury salt and in addition can be directly applied to tissue. They are used to disinfect instruments and as antiseptics on cutaneous and mucosal surfaces. Metaphen has been injected intravenously but it is doubtful whether the drug is effective by this route. The following table indicates the concentrations of merthiolate and metaphen commonly employed.

	Merthiolate	*Metaphen*
Instruments	1:1000	1:5000–1000
Eye	1:10,000–5000	1:10,000–5000
Nasal Mucosa	1:5000–2000	1:5000–2500
Urethra	1:30,000–5000	1:10,000–5000
Skin	1:1000 (tincture)	1:5000–1000

Metaphen is available in aqueous solution in the strength of 1:500 and 1:2500, and as a 1:200 tincture. Merthiolate is marketed in both an aqueous solution and tincture in the concentration of 1:1000, in ointment form (1:2000), as an ophthalmic ointment (1:5000) and in suppositories (1:1000). Merphenyl nitrate is dispensed in a 1:1500 solution. Meroxyl can be obtained in tablets containing 0.15 gram of the drug.

Table 44

THE BACTERICIDAL ACTIVITY OF MERCURIC CHLORIDE AND SEVERAL ORGANIC MERCURIALS

Highest Dilution of Disinfectant Killing Microorganisms after a Ten Minute but not after a Five Minute Contact at 37 C.

(Birkhaug, 1933.)

Microorganism	Phenylmercuric Nitrate	Merthiolate	Metaphen	Mercurochrome	Mercuric Chloride
Staph. Aureus	1:192,000	1:120,000	1:140,000	1:160	1:16,000
Str. hemolyticus	1:144,000	1:112,000	1:110,000	1:320	1:32,000
Pneum. type I	1:96,000	1:64,000	1:72,000	1:240	1:20,000
E. coli	1:48,000	1:32,000	1:32,000	1:180	1:10,000
Gonococcus	1:80,000	1:48,000	1:48,000	1:240	1:20,000
B. subtilis	1:65,000	1:24,000	1:36,000	1:300	1:12,000

Silver Compounds

Silver compounds are widely employed as caustics, astringents, antiseptics and germicides. They owe their properties to the activity of the silver ion which is a protein precipitant. There are two types of silver preparations, the simple soluble silver salts which readily ionize in solution and the colloidal preparations in which silver does not exist to any great extent as free ions. The two classes of silver-containing preparations vary greatly in their pharmacological activity. Only the local actions of silver are discussed, the systemic effects of metallic silver being presented under the metals.

Mechanism of Action. The silver ion is directly toxic to microorganisms by precipitating the protein of the bacterial protoplasm. Active silver compounds exert the same action on body tissues. In fact so destructive is the action of ionic silver on tissues that the preparations of silver which readily ionize must also be classified as caustics and corrosives as well as germicides. There are two phases of the action of silver salts. (1) Solutions of the simple silver salts which ionize have an immediate germicidal and irritant action due to the precipitation of protein by the free silver ion. (2) There then follows a more sustained antiseptic action due to the fact that the silver proteinate formed in the aforementioned reaction slowly liberates a small amount of ionic silver. Colloidal silver preparations, inasmuch as they contain little silver in the ionic form, exert only the second type of action.

Germicidal Efficiency. Simple silver salts are highly germicidal in solution. For example, silver nitrate destroys most microorganisms in a concentration of 1:1000. Much higher dilutions are bacteriostatic. The colloidal silver compounds, however, exert little bactericidal effect. None of the group is germicidal in a concentration of one per cent, but 10 per cent solutions are lethal to microorganisms. However, colloidal silver preparations are bacteriostatic in concentrations up to 1:20,000 (Leonard, 1931).

An interesting bacteriological phenomenon is the fact that distilled water becomes markedly bactericidal after contact with metallic silver. Despite the fact that the concentration of silver ions reaches only one part in 20,000,000, heavy suspensions of bacteria succumb within a few hours. In fact metallic silver can be used for the disinfection of water, but the procedure is expensive. This action of silver is shared by many heavy metals and is known as the *oligodynamic action*. It is probable that in the use of simple salts of silver as antiseptics some metallic silver is obtained by reduction and that the oligodynamic action contributes to the bacteriostatic effect.

Simple Silver Salts

The simple ionizable salts of silver which are employed medicinally are *silver nitrate, silver lactate* and *silver picrate.*

Silver Nitrate. *Silver Nitrate,* U.S.P., B.P., consists of colorless crystals freely soluble in water. It is the most commonly employed of the simple silver salts and is used as a caustic, germicide, antiseptic and astringent. The degree of action depends upon the concentration employed and the period of time during which the compound is allowed to act. The silver ion is readily precipitated by chloride. Thus the action of the silver salts can be readily stopped by washing with a solution of sodium chloride. Also this chemical property accounts for the fact that solutions of simple salts of silver do not readily penetrate into tissues, for the silver ion is precipitated by the chloride of the tissue fluids. Silver salts stain tissue black due to the deposition of reduced silver. The stain slowly disappears spontaneously.

Therapeutic Uses. Silver nitrate is employed either in solid form or in solution. In the form of *fused silver nitrate* (*lunar caustic*) the compound is used for the cauterization of wounds and for removing granulation tissue, warts, etc. It is conveniently dispensed in pencils which should be moistened before use. Solutions of silver nitrate, in strengths of from 0.01 to 10 per cent, are also employed for local application. The concentration is varied depending upon the sensitivity of the tissue exposed and the result desired. For example, a 1:10,000 concentration is employed as a mildly antiseptic and astringent solution for irrigation of the bladder and urethra. When a strongly germicidal action is desired, as for local treatment of infected ulcers of the mouth, a ten per cent solution may be carefully applied. Silver nitrate is also employed in conjunction with tannic acid for the treatment of burns (page 776).

Silver salts are particularly germicidal for gonococci, and silver nitrate is routinely employed (usually required by State law) for the *prophylaxis of ophthalmia neonatorum* in newborn infants. A few drops of a one or two per cent solution are instilled in the conjunctival sac. If the stronger solution is used, the eyes should be washed immediately with an isotonic sodium chloride solution.

Silver Lactate. *Silver Lactate,* N.N.R., is another simple ionizable silver salt. It consists of a white, crystalline powder soluble 1:15 in water. The compound is employed for the same purposes as silver nitrate and is used in dilutions varying from 1:100 to 1:2000.

Silver Picrate. *Silver Picrate,* N.N.R., is an ionizable salt of silver which combines the antiseptic properties of the silver and picrate ions. The compound is a yellow, crystalline powder which is but sparingly soluble in aqueous and organic solvents. Silver picrate has found its chief application in the treatment of *vaginitis,* especially vaginal *trichomoniasis* and *moniliasis.* It is most effectively administered in powder form, five grams of a compound powder containing one part silver picrate and 99 parts purified kaolin being applied to the vaginal wall by means of insufflation (Shelanski, 1939). Supplementary treatment consists in the use of silver picrate vaginal suppositories. Suppositories are marketed which contain 130 mgm of silver picrate in a boroglyceride gelatin base. Silver picrate has also proved effective in the treatment of *trichomoniasis, moniliasis* and *gonorrhea* in the male (Knight and Shelanski, 1939). Four cc of a 0.5 per cent aqueous solution are instilled into the urethra. Gonorrheal vulvovaginitis in children has also been successfully treated with silver picrate suppositories (Holmes and coworkers, 1939).

If silver picrate is employed over extended periods of time there is danger of argyria (page 753) or renal damage from the picrate ion (page 834). The patient should therefore be carefully observed during the therapeutic regimen.

Colloidal Silver Preparations

The colloidal silver preparations contain high concentrations of silver, but for the most part the silver is present in a non-ionized form. Solutions therefore do not precipitate chlorides or protein and penetrate tissues much more readily than do the solutions of the simple silver salts. Colloidal silver solutions, however, are more antiseptic than germicidal. They are also non-corrosive, non-irritant and non-astringent. The one organism that is highly susceptible to the colloidal type of silver solution is the gonococcus which is killed by a short exposure to a 0.5 per cent concentration of mild silver protein or a 0.25 per cent concentration of strong silver protein (*see* preparations).

Classification of Preparations. Many types of silver compounds can be placed in "colloidal solution," and there is a wide variety of commercial preparations available. Colloidal solutions are not true solutions but rather consist of permanent suspensions of insoluble particles of ultramicroscopic size. Colloidal silver solutions vary greatly in their silver content. It is important to remember that the antiseptic activity of a given preparation is not related to the total content of silver, but rather is a function of the concentration of free silver ions. Thus a preparation containing a relatively low amount of silver may be more actively antiseptic or germicidal than one containing a much higher amount of the metal.

The colloidal silver preparations may be conveniently classified into three important groups. These are (1) protein silver, strong type; (2) protein silver, mild type; (3) silver halides. In the following section the characteristics of each group and the preparations contained therein are discussed.

Preparations. *Protein Silver, Strong Type.* Strong protein silver compounds contain the lowest percentage of silver but in solution liberate the highest concentration of silver ions of all the groups. Preparations of this type are intermediate in action between solutions of simple silver salts and the other colloidal silver solutions, have the strongest germicidal action of all the colloidal preparations, and are somewhat irritant. They consist of soluble silver-protein complexes and it is highly probable that most of the silver ionizes in solution. The outstanding preparation in this class is *Strong Protein Silver* (*Strong Silver Protein, Strong Protargin*), U.S.P., the analogous B.P. compound being *Silver Protein* (*Strong Protein Silver, Silver Proteinate*). It consists of a brown, odorless, somewhat hygroscopic powder which is freely soluble in water and contains between 7.5 and 8.5 per cent silver. *Protargol,* N.N.R., is a trade-marked preparation of this same type. Solutions of strong protein silver should be freshly prepared and protected from light. Upon standing, the concentration of silver ions decreases and activity diminishes (Sollmann and Pilcher, 1924).

Protein Silver, Mild Type. The representative member of this type of preparation is *Mild Protein Silver* (*Mild Silver Protein, Mild Protargin*), U.S.P. The compound contains 19 to 25 per cent of silver, and consists of dark brown shining scales which are freely soluble in water. It is prepared by the interaction of protein and silver oxide and only a small fraction of the contained silver is ionizable. Mild protein silver is non-irritant and in fact is somewhat demulcent. Solutions are

Table 45

THERAPEUTIC USES AND DOSES OF PROTEIN SILVER
(N.N.R., 1940.)

Uses	Strong Protein Silver	Mild Protein Silver
	Per cent	Per cent
Eye		
Conjunctivitis, simple, purulent or gonorrheal	2 to 10	Solution, 25 Ointment, 10
Prophylaxis against ophthalmia neonatorum	2 to 10	25
Prophylaxis before ophthalmic operations (several days)		25
Corneal ulcers		50
Nose and Throat	0.5 to 10	Spray, 10 to 20 Swab, 25 to 50
Wounds and Ulcers		1 to 10, solution or ointment 10, dusting powder
Gonorrhea		
Injections—Prophylactic	2	10
Acute	¼ to 1	3 to 10
Chronic	2 to 10	10 to 20
Urethral irrigation	1:2000 to 1:1000	1:1000
Urethral suppositories	5 to 10	20(0.13 Gm. or 2 grains)
Cystitis		20 to 50 (5 cc) or 10 to 25 (30 cc) left in the bladder
Gynecologic Practice		
Solutions	2 to 10	25 (tampons of solution in glycerin)
Tampons	2	
Ointments	5	
Suppositories	5	Suppositories, 20 (0.3 Gm. or 5 grains)
Rectal Administration		
Irrigation	0.1	0.1 to 1
Injection	2	10
Suppositories	5 to 10	20 (0.13 Gm. or 2 grains)

antiseptic rather than germicidal. Trademarked preparations of mild protein silver included in N.N.R. are *Argyn, Cargentos, Silvol* and *Solargentum.* Solutions should be freshly prepared and protected from light. Upon standing, the concentration of ionic silver increases and may triple within one month (Sollmann and Pilcher, 1924).

Silver Halides. Preparations in this class consist of a silver halide in a suitable vehicle. Two such preparations are included in N.N.R. *Lunosol,* N.N.R., consists of a white, granular powder containing 10 per cent silver chloride and 90 per cent sucrose. The compound freely forms colloidal solutions which appear bluish white in reflected light and reddish in transmitted light. *Neo-Silvol,* N.N.R., is a pale yellow, granular substance which contains approximately 20 per cent silver iodide in a base of gelatin. In concentrations up to 50 per cent in water, neo-silvol forms almost colorless, milky or opalescent solutions. Neither of the above preparations precipitates protein or irritates tissues, and both are probably germicidal only in high concentration. They are approximately equal in activity to mild protein silver and possess the advantage, unique among the various types of silver preparations, of not staining.

Therapeutic Uses. The colloidal silver preparations are extensively employed as antiseptics, their site of application being largely restricted to mucous membranes. The sites to which the compounds are most frequently applied are the nose and throat, conjunctivae, urethra, bladder and colon. The purposes for which they are employed include upper respiratory infections, conjunctivitis due to a variety of organisms, the prophylaxis and treatment of gonorrhea, and cystitis. The compounds have also been used in colonic irrigations in the treatment of bacillary dysentery. Colloidal silver preparations are probably of outstanding value only in the treatment of gonococcal conjunctivitis and gonorrhea. In the prophylaxis of gonorrhea they are effective if injected into the urethra within a few hours after exposure. The concentrations of strong and mild protein silver used for various purposes are depicted in Table 45, taken from N.N.R. (1940).

The indiscriminate use of colloidal silver solutions, especially in the prophylaxis and treatment of upper respiratory infections, is probably capable of doing more harm than good. Although an antiseptic action may be desirable in preventing the spread of infection, colloidal silver solutions are not incapable of injuring tissue cells. There is no acceptable evidence that the routine use of silver solutions for the prophylaxis of colds is at all efficacious, and cases of argyria have resulted from this use.

Zinc Salts

The salts of zinc are astringents, corrosives and mild antiseptics. They owe their action to the ability of the zinc ion to precipitate protein. The soluble salts of zinc which ionize most completely, such as zinc chloride, are quite irritating and can be used as escharotics. When taken internally, the irritation of the gastric mucosa produced by the zinc salts causes vomiting, and zinc sulfate has been employed as an emetic. Otherwise the main use of the salts of zinc is for their astringent and antiseptic action on mucous membranes and skin.

Zinc Sulfate, U.S.P., B.P., Zinc Acetate, U.S.P., Zinc Chloride, U.S.P., B.P. These salts are all water soluble and are usually employed in aqueous solution. Zinc sulfate is commonly employed as an astringent and antiseptic whereas zinc chloride is used when the more powerful escharotic action is desired. Zinc sulfate and acetate are used as eye washes (0.1 to 1.0 per cent) in *conjunctivitis* caused by the *Morax-Axenfeld bacillus.* They are also employed in *gonorrheal urethritis* (0.5 to 4.0 per cent), but they should not be used until the infection is well under control because the antiseptic action is not sufficiently great and the elimination of discharge brought about by the astringent effects of the salts gives the patient a false sense of security. If used early, they should be alternated with more powerful germicides. For application to the skin, zinc sulfate is used in a concentration of four per cent. It is often incorporated with sulfurated potash in equal concentration in an ointment known as *Lotio Alba* (*White Ointment*), N.F. Zinc Sulfate is useful in such skin diseases and infections as *acne, ivy poisoning, lupus erythematosus* and *impetigo.* The compound also forms the basis for most of the deodorant anhidrotics.

Zinc sulfate has been employed in solution in a nasal spray as a prophylactic astringent against *poliomyelitis.* A one per cent solution incorporated with 0.5 per cent sodium chloride and 1.0 per cent pontocaine is used. The value of an astringent solution in the prophylaxis of poliomyelitis has not yet been established. A nasal spray of zinc sulfate has also been used to shrink the mucous membranes to allow drainage from infected accessory nasal sinuses. Treatment of this type has a disadvantage in that it inhibits the activity of the cilia of the respiratory mucous membrane.

Zinc Oxide, U.S.P., B.P. This is a fine, white, insoluble salt of zinc which is incorporated in powders, ointments and pastes. It has a mild astringent and antiseptic action. It is used in skin diseases and infections such as *eczema, impetigo, ringworm, varicose ulcers, pruritus* and *psoriasis.* Official preparations containing zinc oxide include *Zinc Oxide Ointment* (*Zinc Ointment*), U.S.P. (20 per cent zinc oxide), B.P. (15 per cent zinc oxide), *Compound Paste of Zinc Oxide,* B.P. (25 per cent zinc oxide), *Paste of Zinc Oxide, Hard Paste of Zinc Oxide, Soft Paste of Zinc Oxide,* N.F. (all 25 per cent zinc oxide) and *Paste of Zinc Oxide with Salicylic Acid,* N.F. (two per cent salicylic acid in paste of zinc oxide). *Prepared Calamine,* N.F., consists of a pink powder containing zinc oxide (not less than 98 per cent) with a small amount of ferric oxide. Official preparations of calamine include *Calamine Lotion,* N.F. (eight per cent calamine), *Phenolated Lotion of Calamine* (*Compound Lotion of Calamine*), N.F. (one per cent phenol in calamine lotion), *Calamine Liniment,* N.F., and *Ointment of Calamine,* N.F. *Zinc Stearate,* U.S.P., B.P., and *Zinc Oleate,* B.P., have actions similar to zinc oxide. Other antiseptic zinc compounds are *zinc permanganate* and *zinc peroxide* which are discussed under oxidizing antiseptics.

Copper

Salts of copper act as germicidal and fungicidal astringents. It was early appreciated that copper is highly toxic to algae, a concentration of 1:1,000,000 being ample to inhibit growth. However, the actions of copper as a bactericide are not as striking. The element possesses an oligodynamic action, but this is not manifest in water which is heavily contaminated. The soluble salts are bacteriostatic in relatively high dilutions, but even five per cent solutions are not toxic to many microorganisms and spores. For example, spores of anthrax resist exposure to molar solutions of copper sulfate (15.9 per cent) for many days.

Copper seemingly is a more effective fungicide than bactericide, and copper salts have some clinical applications in the treatment of fungus infections. In the form of Bordeaux mixture, copper is widely employed as a plant fungicide.

Copper salts are irritant and astringent. When solutions are taken by mouth, prompt emesis occurs and copper salts have been employed as emetics (page

814). Large amounts taken orally can cause the usual symptoms of corrosive poisoning. If an appreciable quantity of the element is absorbed, symptoms of systemic toxicity may appear, copper apparently being a neuromuscular poison. This rarely occurs, however, due to the prompt emesis.

Copper in small amounts is a normal constituent of the diet and can be detected in the blood. Its physiological rôle is apparently concerned chiefly with hematopoiesis (page 1117).

Copper Sulfate, U.S.P., B.P., is the only official salt of copper. It occurs as a deep blue crystalline powder, readily soluble in water. Copper sulfate has been employed clinically as a fungicide. Haggard, Strauss and Greenberg (1939) reported good results in the treatment of *epidermophytosis* by the use of copper administered by iontophoresis. For local application to opened vesicles, a 0.4 per cent solution of copper sulfate may be used. Copper sulfate has also been employed in the treatment of *chancroid ulcer,* a 10 to 25 per cent solution being applied to the lesion for a few minutes following preliminary anesthetization. The salt has been used for its systemic action in the therapy of *blastomycosis,* fifteen to 60 mgm being given orally three times daily. There are several reports of the use of 1:5000 solutions of copper sulfate as retention enemas in the treatment of *bacillary* and *amebic dysentery.* An ointment of copper citrate (five to 10 per cent) has been employed in the treatment of *trachomatous conjunctivitis.*

DYES

The synthetic organic dyes or so-called "coal-tar" dyes are valuable therapeutic agents in medicine and surgery. They are employed as antiseptics, chemotherapeutic agents against protozoa and wound healing agents, and they also have a special field of usefulness in certain diagnostic procedures for the determination of renal and hepatic functions. The medicinal importance of the organic dyes was appreciated after Churchman (1912) observed the effect of gentian violet on Gram-positive organisms and Ehrlich in the same year introduced acriflavine as a bactericidal agent.

Basis of Action. The antiseptic dyes have a marked specificity of action which seemingly is related to the staining properties of bacteria. The staining properties in turn are dependent upon physico-chemical characteristics of the constituents of the bacterial cells. Therefore it is believed that the bactericidal action of the antiseptic dyes is closely related to the physico-chemical properties of the compounds. Antiseptic dyes can be divided into two groups depending upon whether the chromogenic radical is electropositive or electronegative. The electropositive dyes have a special affinity for the Gram-positive organisms, are more active in a basic medium and are called the basic dyes. This does not mean that the compounds themselves are basic but rather they have an affinity for chemically basic groups. The acid dyes are active against Gram-negative organisms and act best in an acid medium.

Other factors than type of organism and pH also influence the activity of germicidal dyes. Their antiseptic properties are greatly diminished in the presence of serum or other organic material. Temperatures higher than that of the body also decrease their effectiveness.

Toxicity. All the antiseptic dyes are toxic to tissue cells as well as to microorganisms. In the case of some compounds the sensitivity of host cells is greater than that of the parasite. However, many of the dyes have a high therapeutic index and several are effective even after intravenous administration.

Classification. There are many ways of classifying the antiseptic dyes but the simplest is on the basis of their chemical constitution. The following chemical classification is that utilized by N.N.R. (1940): (1) azo dyes, (2) acridine dyes, (3) fluorescein dyes, (4) phenolphthalein dyes, (5) triphenylmethane or rosaniline dyes, and (6) miscellaneous dyes. They will be discussed in this order.

Azo Dyes

Actions and Therapeutic Applications. The azo dyes are not used as antiseptics but rather as wound-healing agents. These compounds seemingly stimulate tissue proliferation and are used in the treatment of burns, wounds, chronic ulcers and bed-sores. They are usually employed in the form of ointments or oily solutions (4.0 to 8.0 per cent). Strong concentrations (eight per cent) are likely to be irritating and in clinical use the azo dyes are usually alternated with a soothing ointment. There is no unanimity of opinion as to their effectiveness and worth. It should be pointed out that the azo dyes very closely approximate certain carcinogenic agents in chemical structure. However, there is no evidence that the compounds used clinically have been the cause of cancer.

Preparations. *Scarlet Red,* N.F., is one of the most widely employed of the azo dyes. The N.N.R. distinguishes between two types of scarlet red, *Scarlet Red Medicinal,* N.F., which chemically is toluylazotoluylazo-beta-naphthol and *Scarlet Red Sulfonate,* N.N.R., which differs from the former chemically in that it is the sodium salt of azobenzenedisulfonic acid azobetanaphthol. Both are brownish-red odorless powders and are used in the same manner. A third azo dye, *Dimazon,* N.N.R., which chemically is diacetylaminoazotoluene, is employed as an ointment or oily solution (two per cent), or as a dusting powder (five per cent in talcum).

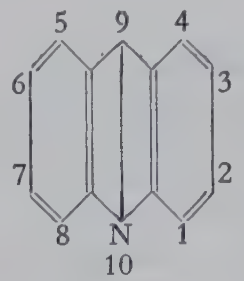
Pyridium. This compound is an azo dye with greater antiseptic activity than the agents previously mentioned. It was introduced for oral use as a *urinary antiseptic.* Although the compound is active *in vitro,* it imparts little bactericidal activity to the urine when ingested, and the Council has reported unfavorably on it. Although a few investigators are impressed with its action, the availability of such effective urinary antiseptics as methenamine, mandelic acid and sulfanilamide has led to the almost complete rejection of pyridium.

Acridine Dyes

The acridine dyes, because of their yellow color, have been termed the "flavines." *Acriflavine,* the first of the group to be studied, was introduced by Ehrlich (1912) under the name "trypaflavine." As the name implies, it was first used against trypanosome infestations. Although the drug possesses some trypanocidal action, its clinical use at present is directed against bacteria rather than protozoa.

Although the acridine dyes are germicides, and occupy an important position among the antiseptic drugs, many of the original claims for these compounds have not been substantiated. When first introduced, it was believed that acriflavine was more potent in the presence of serum than in simple solution and such statements still appear in the literature. This unique property would obviously add greatly to its therapeutic value. However, Eggerth (1926) demonstrated that the potentiating effect of serum *in vitro* was due to the fact that this fluid becomes quite alkaline as carbon dioxide is given off. Inasmuch as acriflavine belongs to the "basic" group of antiseptic dyes, an alkaline medium greatly favors its action. If the bactericidal action of acriflavine is tested in serum and precautions are taken to prevent the loss of carbon dioxide from the medium, no potentiation of activity can be observed. It was also claimed that the acridine dyes are much less toxic to tissue than other compounds of equal bactericidal activity. This has not been substantiated by carefully controlled experiments.

Chemistry. The acridine dyes are amino derivatives of acridine. The basic acridine structure appears as follows:



Acridine

Acriflavine base is a mixture of 2,8 diamino acridine and 2,8 diamino-10-methyl chloride acridine. *Acriflavine hydrochloride* contains HCl on one of the amino groups. *Proflavine* is 2,8 diamino acridine hydrogen sulfate, the hydrosulfate being on the nitrogen in the 10 position. Seemingly the position of the amino groups largely determines the antibacterial activity of this class of compounds. The chemical relations between structure and action of the amino-acridines have been closely studied by Albert, Dyer and Linnel (1937, *et seq.*). They prepared the compound 2,7 diamino acridine which was observed to be equal in antiseptic activity to proflavine and acriflavine, but to be only two-fifths as toxic as the former and one-tenth as toxic as the latter. Acriflavine is more toxic and more germicidal than proflavine, but proflavine appears to have a more rapid onset of action.

Preparations. *Acriflavine* (*Acriflavine Base, Neutral Acriflavine*), U.S.P., is a brownish-red water-soluble powder and is available in 0.1 gram tablets, in ampules for intravenous injection, in jelly (1:1000) and ointment (one per cent) form and in 30 mgm enteric-coated tablets for oral use. *Acriflavine Hydrochloride,* U.S.P. (*Acriflavine,* B.P.), is a brownish-red water-soluble powder and is available in 30 mgm tablets. *Proflavine,* N.N.R., is a reddish-brown water-soluble powder and is available in tablet form.

The acridine dyes are stable to heat but relatively unstable to light. They should be kept in amber-colored glass containers and solutions should be discarded after one week.

Pharmacological Actions. The flavines are effective germicides against Gram-positive microorganisms when acting in an alkaline medium. The gonococcus is especially susceptible. The ingestion of the acridine dyes leads to the excretion of appreciable amounts in the urine, and the compounds are rather effective urinary antiseptics if the reaction of the urine is kept alkaline.

The flavines are not without systemic effects. The toxic intravenous dose for animals is approximately 30 mgm per kilogram. Continued administration of subtoxic doses leads to pathological changes in the liver and kidneys (Heathcote and Urquhart, 1930). Small doses are said to affect the peripheral vagal mechanism of the heart (Crittenden, 1932).

Therapeutic Uses and Dosage. Although the acridine dyes were originally introduced as trypanocides, they are now used almost exclusively as bactericides.

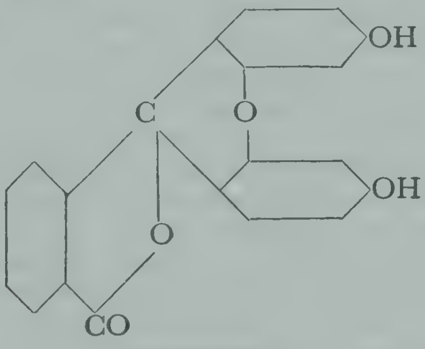
In the treatment of *wounds*, a 1:1000 solution dissolved in physiological saline is employed for washing and for gauze packing. For small open wounds, ointments may be employed. For application to the *mucous membranes* of the nose and throat, a 1:1000 solution may be used. In the treatment of *gonorrhea*, a 1:1000 solution may be injected into the urethra, but if large quantities are used for irrigation the strength should be reduced to 1:4000 to 1:10,000. In *suppurative infections* of the middle ear and mastoid, a 1:500 solution in 50 per cent alcohol may be employed as drops or to saturate a gauze pack.

The acridine dyes have been used as *urinary antiseptics* but have largely been replaced by more effective compounds. They are given in capsule form in a dose of 0.2 gram daily. The urine should be kept alkaline in order to assure optimal activity. Favorable results are obtained when the invading organism is either *E. coli* or *staphylococci*. Unpleasant side-actions are nausea and catharsis. The intravenous injection of the acridine dyes in *septicemia* is probably a futile procedure and not without danger.

Fluorescein (Pyronine) Dyes

There are only two fluorescein dyes of clinical importance, *fluorescein* and *mercurochrome*. Fluorescein is not an antiseptic dye but is used as a diagnostic agent in ophthalmological work to delineate corneal ulceration and foreign bodies. Mercurochrome is a combination of mercury and fluorescein, and its antiseptic activity can be largely attributed to the mercury. Mercurochrome is discussed under the antiseptic mercury compounds.

Chemistry. Fluorescein is chemically related to the phenolphthalein dyes. It is a combination of resorcinol with phthalic anhydride and has the following structural formula.



Fluorescein

In alkaline solution, the sodium salt of the above compound is formed and this has a quinoid structure which imparts the color.

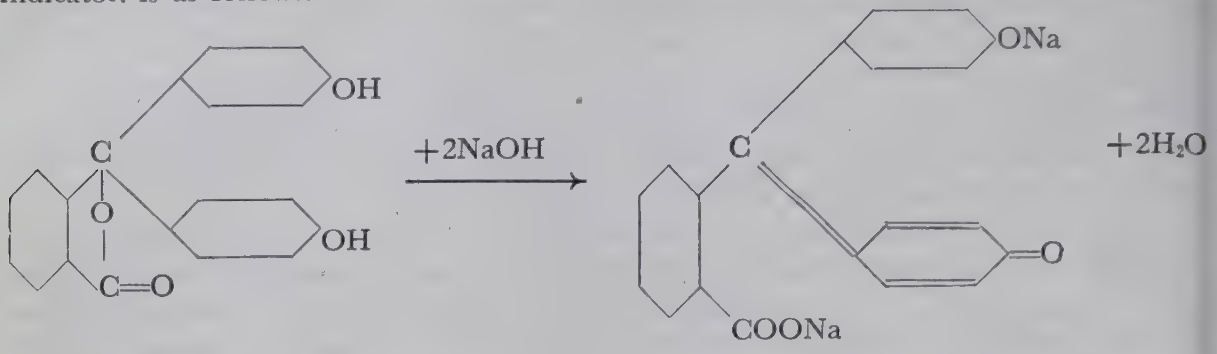
Preparations. *Fluorescein*, N.N.R., is an orange-red powder insoluble in water. Solutions of the sodium salt are formed by dissolving two grams of fluorescein and three grams of sodium bicarbonate in sufficient water to make 100 cc. This solution is red by transmitted light, but has a green fluorescence by reflected light. *Fluorescein Soluble,* B.P., is the sodium salt of fluorescein. It is an orange-red water-soluble powder.

Therapeutic Use. When a solution of the sodium salt of fluorescein is applied to the cornea, only those portions deprived of epithelium are stained. Ulcerated areas are stained green; foreign bodies appear surrounded by a green ring; and loss of substance in the conjunctiva is indicated by a yellow stain.

Phenolphthalein Dyes

The phenolphthalein dyes are not antiseptic, and are used mainly as diagnostic agents.

Chemistry. The structure of phenolphthalein is similar to that of fluorescein, being a combination product of phthalic anhydride and phenol. In acid solution the compound is colorless, but in alkaline solution a quinoid structure is obtained which results in an intense red coloration. The reaction, which accounts for the value of phenolphthalein as an indicator, is as follows:



Preparations and Uses. *Phenolphthalein,* U.S.P., B.P., is a colorless powder, insoluble in water but soluble in alcohol. It is used in the laboratory as an indicator and medicinally as a cathartic (page 802). *Bromsulphalein,* N.N.R., is the sulfonated derivative of the interaction product of tetrabromphthalic anhydride and phenol. It is obtained as the disodium salt (five per cent solution) and used for the determination of liver function. The drug, in five per cent solution, is injected intravenously in the dose of 2.0 mgm per kilogram of body weight. Thirty minutes later a sample of blood is withdrawn and the dye content of the alkalinized serum determined by colorimetric comparison with a series of standards. The normal liver excretes most of the dye within a thirty minute period (Figure 6).

Phenolsulfonphthalein, U.S.P. (*Phenol Red*), which differs from phenolphthalein in that it has an SO_2 instead of a CO grouping in the phthalic anhydride portion of the molecule, is obtained as the monosodium salt. It is used in the testing of renal function. Six mgm of the dye are given by intramuscular or intravenous injection. The urine is collected over suitable intervals (usually 70 and 120 minutes after intramuscular injection, 15 or 30 and 60 minutes after intravenous injection) and the dye content of the voided samples is determined colorimetrically. For the determination, the urine is made alkaline, diluted to a volume of one liter and compared with standards. The normally functioning kidney excretes approximately the following portions of the injected dye: intravenous administration—35 to 45 per cent in 15 minutes, 50 to 60 per cent in 30 minutes, 65 to 80 per cent in 60 minutes; intramuscular administration—60 to 80 per cent in 120 minutes. Functional renal insufficiency is evidenced by a failure to excrete the amounts of the dye cited. Inasmuch as some of the dye is excreted by the bile, supranormal values are suggestive of hepatic insufficiency.

Phenoltetrachlorphthalein, N.N.R., made from tetrachlorphthalic anhydride and phenol, is marketed in ampules containing a solution of the disodium salt and is used for determining the functional activity of the liver. The dose is from 0.05 to 0.4 gram of the drug given by intravenous injection. The principles of the technic are the same as for the bromsulphalein test.

Soluble Iodophthalein, U.S.P., B.P., the disodium salt of tetraiodophenolphthalein, and *Phentetiothalein-Sodium,* N.N.R., the disodium salt of phenoltetraiodophthalein, are both used for the roentgenological examination of the gall bladder. Soluble iodophthalein is given in the dose of 3.0 grams for patients weighing from 115 to 160 pounds and 3.5 grams for patients over 160 pounds. The total dose is made up as a 12.5 per cent aqueous solution and divided into two portions which are injected intravenously 30 minutes apart. The drug may also be given by mouth in enteric-coated capsules. The oral dose is 4.0 grams. Untoward reactions to intravenous administration include dizziness, nausea, various body pains and transient fall in blood pressure.

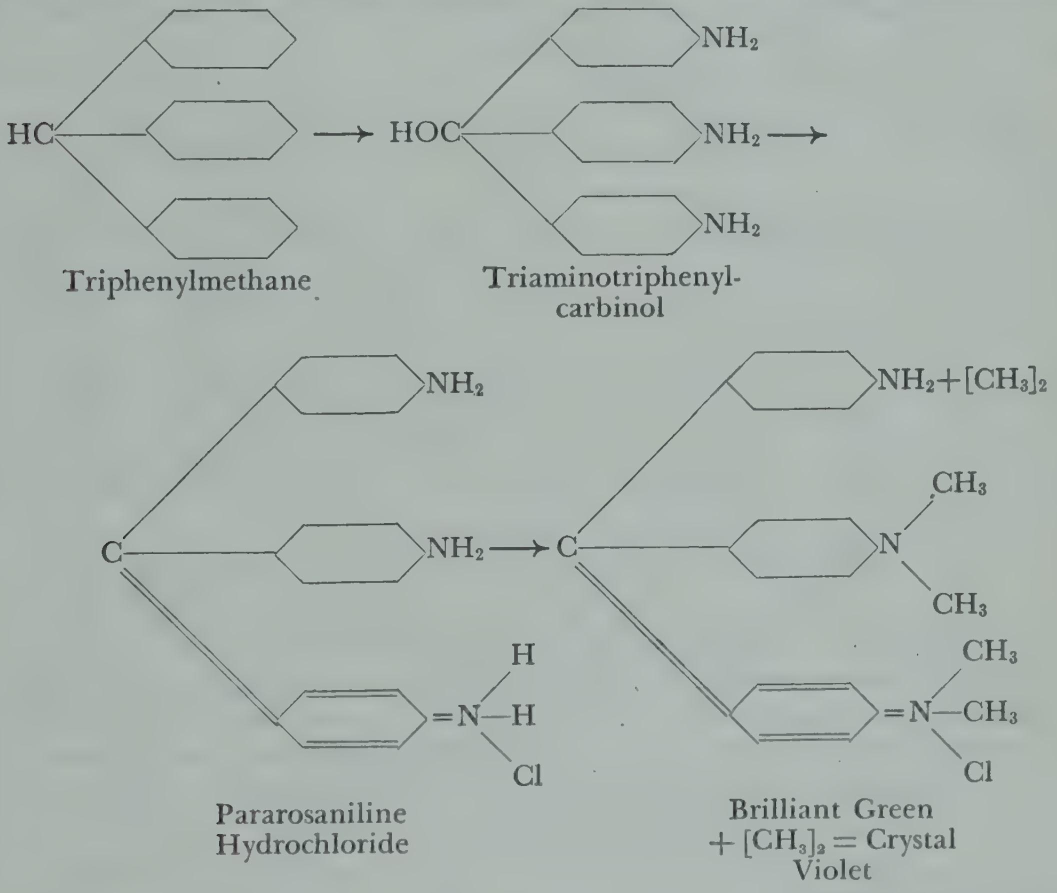
Phentetiothalein is unique in that the compound is suitable for simultaneous cholecystography and determination of liver function. The drug is given by intravenous injection (eight per cent solution) in the dose of 40 mgm per kilogram. The total dose need not exceed 2.5 grams regardless of body weight. The presence of dye in the blood is determined colorimetrically 30 and 60 minutes later. If only cholecystography is desired, the drug may be given orally in gelatin capsules in a dose of 4.0 grams, but the roentgenological results are more satisfactory after intravenous injection of the dye.

The possibility that iodophthalein may be effective in the treatment of carriers of the typhoid-paratyphoid group of bacteria has been suggested by Saphir and Howell (1940). They report a case in which the oral administration of iodophthalein was followed by immediate disappearance of *paratyphoid A* bacilli from the stool. Four doses (four grams each) were administered orally at weekly intervals, the stools remaining free from the organism for the period of observation (seven months). That a typhoid carrier may harbor the organisms in his gall bladder offers a partial explanation for the efficacy of iodophthalein, but Saphir and Howell could observe no bactericidal action of the dye, even in the presence of bile.

Triphenylmethane (Rosaniline) Dyes

The triphenylmethane or rosaniline dyes are a group of basic dyes which are effective germicides against Gram-positive organisms. The group includes gentian violet, crystal violet, methyl violet, brilliant green and acid and basic fuchsin. The first four are used medicinally.

Chemistry. As the name implies, the dyes are derivatives of triphenylmethane. In their synthesis, triphenylmethane is converted to triaminotriphenylcarbinol and when the anhydride of the hydrochloride salt is formed the resulting compound, pararosaniline hydrochloride, has the quinoid structure which endows this type of compound with color. If methyl groups are now introduced into the amino radicals of pararosaniline hydrochloride, the compounds listed above are obtained. Thus brilliant green has four methyl groups, methyl violet five, crystal violet six, and gentian violet is a mixture of pararosaniline derivatives containing five and six methyl groups. The chemical relationships can be depicted as follows:



Triphenylmethane

Triaminotriphenylcarbinol

Pararosaniline Hydrochloride

Brilliant Green + $[CH_3]_2$ = Crystal Violet

Pharmacological Actions. The rosaniline dyes are bactericidal to Gram-positive microorganisms in dilutions of approximately 1:1,000,000. They are particularly effective against *staphylococci, B. diphtheriae,* and *B. pyocyaneus.* Also the causative organism of Vincent's angina, and many strains of monilia, torula, epidermophyton and trichophyton are susceptible to this group of dyes. Gentian violet is also an effective anthelmintic. The Gram-negative bacteria are very resistant to the rosaniline dyes. Also acid-fast organisms, although they take the Gram stain, are little affected. In fact the incorporation of gentian violet in the medium facilitates the isolation of *Myobacterium tuberculosis* from tissue infected with Gram-positive organisms.

The rosaniline dyes form a precipitate with necrotic tissue. This property is of unique value in the treatment of burns.

Preparations. *Gentian Violet Medicinal,* N.N.R., is available in powder form and in enteric coated capsules (32 mgm). *Crystal Violet,* N.N.R., a water-soluble dark green powder, can be obtained in powder form and also as a jelly containing one per cent of the dye in a gum tragacanth base. *Methyl-rosaniline,* N.F. (*Gentian Violet, Methyl Violet, Crystal Violet*), is predominantly hexamethylpararosaniline chloride admixed with the pentamethyl and tetramethyl derivatives. It is a dark green powder soluble 1:25 in water. *Brilliant Green* has not been used as extensively as the above dyes, is not an official drug and has not as yet been included in N.N.R. It can be obtained, however, and has been employed in the treatment of burns. It has also had sporadic trials in the treatment of skin disorders and infections, including erysipelas.

Therapeutic Uses and Doses. Gentian violet and crystal violet are employed in the control of many types of infections. Although gentian violet is the older and more popular preparation, it is probable that these two compounds are identical in action and therapeutic efficiency.

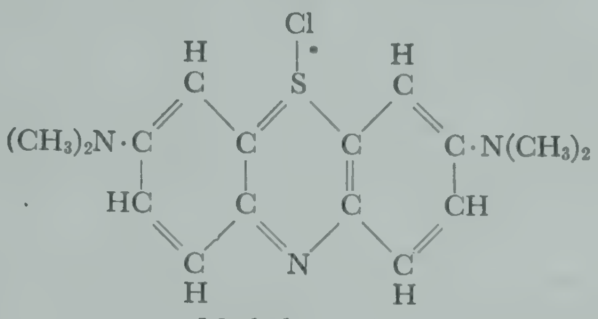
For direct application to tissues the dyes are used in a concentration of 1:500 to 1:1000. For instillations in closed cavities the concentration is reduced to 1:10,000. They may be used for infected wounds, mucous membranes and serous surfaces. Sutton (1938) reported two cases of tatooing of the skin which resulted from contact of gentian violet with granulation tissue and advises that the dye not be applied to ulcerative lesions of the face. Specific conditions for which these dyes have been employed include *empyema, suppurating joint, cystitis* and *urethritis, Vincent's angina, infectious eczematoid dermatitis, infantile eczema, furunculosis, recurrent dermatomycoses, monilial paronychia, chronic ulcers* and *bed sores, impetigo infectiosa, pruritus ani* and *pruritus vulvae,* etc. (*See* review of Sutton, 1938.) Gentian violet has also been used as an anthelmintic in the treatment of *Strongyloides* and *Oxyuris infestations* (page 896). The use of gentian violet in the treatment of *burns* is discussed on page 776.

The intravenous administration of gentian violet in the dose of five mgm per kilo, given in 0.5 per cent solution, has been recommended for the treatment of such conditions as *staphylococcal septicemia* and other systemic infections from Gram-positive organisms that cannot be treated locally. Although the drug is nontoxic when applied repeatedly to body surfaces, it sometimes produces alarming reactions when injected directly into the circulation. These are probably the result of flocculation and colloidal "reactions." The value of intravenous therapy with gentian violet has not been well established. Patients injected with the dye show a blue coloration of the skin over a period of several hours which produces a cyanotic appearance.

Methylene Blue

Methylene blue was the first of the antiseptic dyes to be used medicinally. It was recommended as an intestinal antiseptic as early as 1890 and in 1891 Einhorn published his results on the efficacy of methylene blue as a urinary antiseptic. It is not a very efficient bactericide, however, and it has largely been discarded.

Chemistry. Methylene blue is tetramethylthionine chloride. It has the following structural formula:



Methylene Blue

The compound can be reduced to colorless or leuko forms, and thus methylene blue and its reduction products comprise a reversible oxidation-reduction system.

Pharmacological Properties. *Bactericidal Actions.* Methylene blue is a weak antiseptic. For example, *E. coli* will survive for 25 minutes in a 1:10 solution of methylene blue. *T. pallidum* is not killed by concentrations of 1:100. *Staphylococci* are more susceptible, a concentration of 1:1000 being bactericidal. Methylene blue is more efficient as a bacteriostatic and seemingly inhibits the growth of *Mycobacterium tuberculosis* in low concentrations.

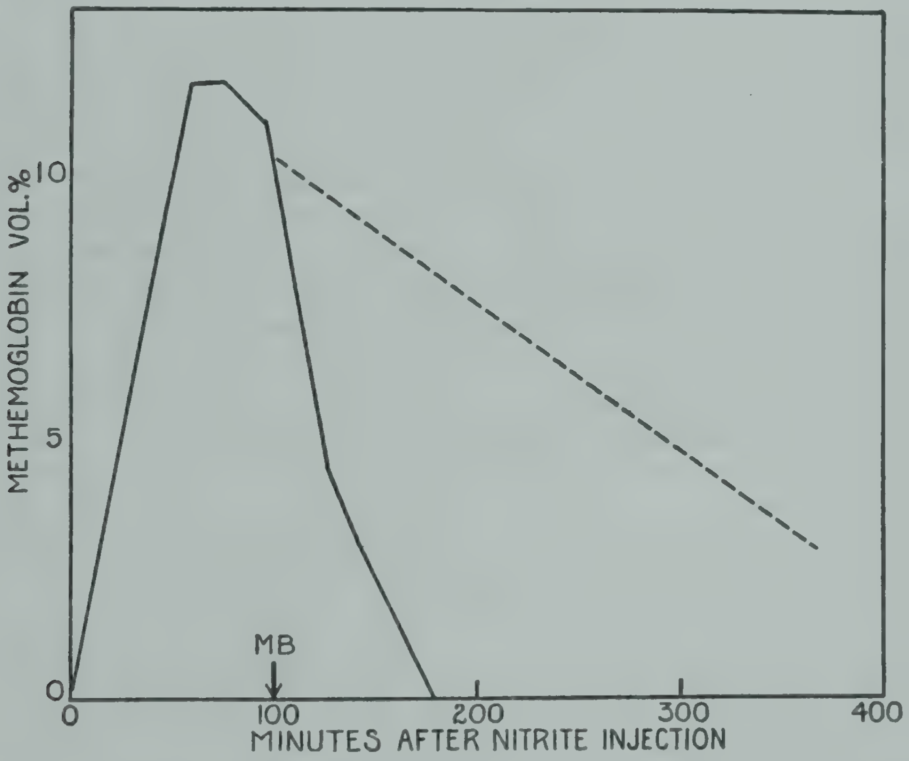


FIGURE 87. *The effect of methylene blue on the rate of conversion of methemoglobin to hemoglobin.*

Methemoglobinemia produced in dogs by the intravenous injection of sodium nitrite (at zero time). Broken line indicates the rate of spontaneous disappearance of methemoglobin from the blood of control animals. The intravenous injection of 2 mgm/kg of methylene blue (at arrow) markedly accelerates the rate of reduction of methemoglobin to hemoglobin. (After Wendel, 1939. Courtesy of the *Journal of Clinical Investigation.*)

Methemoglobin Formation and Reconversion. Methylene blue has two interesting and opposite actions on hemoglobin. In high concentrations it converts the ferrous iron of reduced hemoglobin to the ferric form and thus methemoglobin is produced. This action is shared by such compounds as aniline, ferricyanide, nitrites, etc., and is the basis for the antidotal action of methylene blue in cyanide poisoning. On the other hand, low concentrations of methylene blue or the chemically related thionine are capable *in vivo* of hastening the conversion of methemoglobin back to the form which once more can carry oxygen (Hauschild, 1937; Wendel, 1937, 1939) (Figure 87). Hauschild believes that the reversible oxidation-reduction system of methylene blue and its leuko form is the explanation for this action.

Untoward Reactions. Certain methylene blue preparations are likely to cause nausea, vomiting and diarrhea. This may in part be the result of their contamination with arsenic and zinc. Despite the fact that the U.S.P. specifies the limitation of the arsenic and zinc content of methylene blue used medicinally, many preparations contain higher amounts than are permissible (Greenberg and coworkers, 1935).

Preparations. *Methylthionine Chloride* (*Methylene Blue*), U.S.P., B.P., consists of dark green crystals which are freely soluble in water and alcohol to form solutions having a deep blue color. The compound is marketed in the powder form and in aqueous solution in ampules. For oral administration, the dye is conveniently given in capsules or coated tablets.

Therapeutic Uses. Methylene blue was formerly used as a *urinary antiseptic,* but has been replaced by such compounds as sulfanilamide, mandelic acid and methenamine. Greenberg and coworkers (1935) claim that it is of special value in the treatment of tuberculosis of the urinary tract. The use of methylene blue as an analgesic, antipyretic and parasiticide has been abandoned. It is of some value as an antidote in *cyanide poisoning* (page 701), but is inferior to the nitrites. There is no rationale for the use of methylene blue in carbon monoxide poisoning, for which unfortunately it has been recommended and employed (page 699). Hartmann and coworkers (1938) and others have reported on the use of methylene blue to reduce or avoid the *methemoglobinemia* attending sulfanilamide medication (page 1032). The results are promising and the dye may prove valuable in the treatment of methemoglobinemia from other agents.

MISCELLANEOUS AGENTS

Sulfur

Sulfur has a long history as a medicinal agent; the practice of burning sulfur for the purification of the air was mentioned in the Odyssey. Hippocrates considered sulfur an effective antidote against plague. For the layman, sulfur has an undeserved reputation as an intestinal antiseptic, and the practice of an annual Spring cleansing of the intestinal tract with sulfur and molasses is still prevalent.

Sulfur has been used by the medical profession for a variety of purposes which extend from its oral administration for the treatment of mental disease to its local application for affections of the skin. Probably the only legitimate use of sulfur is as a fungicide and for the treatment of various cutaneous diseases.

Germicidal and Fungicidal Actions. Sulfur itself is not highly toxic to microorganisms, but rather must be converted to some other form to be active. Investigations attempting to elucidate the mechanism of action of sulfur have for the most part been conducted by plant pathologists in connection with the fungicidal properties of the element. The medical profession, in the main, has accepted sulfur on an empirical basis. The two compounds to which the fungicidal activity of sulfur has been attributed are hydrogen sulfide and pentathionic acid ($H_2S_5O_6$). Pentathionic acid is an oxidation product of sulfur which has been shown experimentally to be both germicidal and fungicidal. Solutions of hydrogen sulfide, on the other hand, have relatively little effect on pathogenic organisms so that it is more likely that pentathionic acid accounts for the therapeutic activity of sulfur. Presumably the oxidation of sulfur to pentathionic acid is accomplished by the microorganisms, or by the cells of the epidermis when the element is applied to the skin. Sulfur also possesses a keratolytic property and this may be the basis for the therapeutic action of the element in skin disorders unassociated with infection. In addition, sulfur is a valuable parasiticide.

Systemic Actions. Sulfur has few outstanding systemic actions. When given orally, elemental sulfur may be partially converted to sulfides and these are sufficiently irritant to the intestinal tract to have a cathartic action. Absorbed sulfides are excreted as sulfates. In certain rare individuals, the absorption of sulfide from the intestine is thought to be associated with the occurrence of episodes of intermittent *enterogenous cyanosis* due to sulfhemoglobinemia. The parenteral administration of colloidal sulfur may cause untoward systemic reactions.

Preparations. *Sublimed Sulfur* (*Flowers of Sulfur*), U.S.P., B.P., is a fine, yellow, crystalline, water-insoluble powder with a faint odor and taste. The compound is rendered odorless and tasteless by washing with ammonia water to yield *Washed Sulfur,* U.S.P. *Precipitated Sulfur,* U.S.P., B.P., is an odorless, tasteless compound which differs from the preparations mentioned in that it is a much finer powder and therefore has a greater reactive surface. *Colloidal Sulfur* has no official status, nor is it included in N.N.R. Colloidal sulfur is the most active form of sulfur. It consists of elemental sulfur in such a minute state of subdivision that it can be placed in aqueous colloidal solution. It can also be incorporated in ointment bases. Preparations are likely to contain a significant amount of pentathionic acid.

There are several official ointments of sulfur. *Sulfur Ointment,* U.S.P., contains 15 per cent precipitated sulfur in a base of wool fat, wax and petrolatum. *Alkaline Ointment of Sulfur,* N.F., contains 20 per cent sublimed sulfur and 10 per cent potassium carbonate in a similar base. The presence of the alkali increases the pentrating power of the ointment. *Compound Ointment of Sulfur,* N.F., another alkaline ointment, contains sublimed sulfur, calcium carbonate, juniper tar, soft soap and solid petroxolin. *Ointment of Sulfur,* B.P., consists of 10 per cent sublimed sulfur in simple ointment base.

Therapeutic Uses. Sulfur is of chief value in the treatment of various skin diseases. The parasiticidal action of the element makes it of value in the therapy of *ringworm infections, scabies* and *pediculosis.* The U.S.P. ointment in full or part strength is suitable for these purposes. In the treatment of scabies, an alkaline ointment is often to be preferred in that it penetrates more effectively into the burrow. In addition, sulfur alone or in combination with other keratolytic agents (often two per cent salicylic acid), is widely used in the treatment of skin disorders such as *psoriasis, seborrhea, eczema-dermatitis, lupus erythematosus,* etc. The percentage of sulfur employed may be that of the full strength ointment or weaker if the patient's skin shows intolerance. Prolonged local use of sulfur may result in a characteristic dermatitis venenata.

Colloidal sulfur has been employed both locally and systemically. Locally, it is effective in all the conditions mentioned. It is used in colloidal solution in water or glycerin, or in a suitable ointment base in concentrations ranging from two to 10 per cent. The applications of colloidal sulfur in dermatology have been summarized by Miller (1935).

Solutions of colloidal sulfur have been administered parenterally in the treatment of a number of diseases. Its extensive use in the therapy of *arthritis* deserves mention. A questionable rationale for the use of the drug is the finding by some investigators that the sulfur content of the hair and nails of arthritic individuals is lower than normal, and the excretion of sulfur in the urine higher. Some who support the use of the drug make the extravagant statement that sulfur therapy causes a cessation of pain, a retrocession of deformities, and an improvement in the function of the joints. However, controlled observations by investigators experienced in the treatment of arthritis fail to support such sanguine claims. Some patients may experience subjective benefit, but probably few show objective improvement.

In the treatment of arthritis, solutions of colloidal sulfur have been administered by the intramuscular and intravenous routes. Unpleasant reactions are likely to occur, and these may include fever, malaise, severe headache, fatigue, drowsiness and a temporary increase in joint pain. The doses that have been employed vary greatly. The status of sulfur in the treatment of arthritis has been reviewed by the Council (1938) and Comroe (1939). The Council report concludes, "Sulfur may have some therapeutic value in affording temporary symptomatic relief in some forms of arthritis, but the literature does not afford evidence concerning the type of cases in which it may be useful. It often induces fever (and other symptoms) but it is not known whether the fever will be useful or harmful in a given case. There is almost a total lack of knowledge concerning the contraindications. The optimum dose has not been determined. It is unsuited for experimental use except in institutions, or under other conditions in which its effects may be followed intelligently and accurately for prolonged periods."

Sulfur Dioxide

Sulfur dioxide is a gas obtained from the combustion of sulfur. The burning of sulfur was at one time extensively practiced for the purpose of *fumigation,* but has been largely abandoned, the gas being a relatively poor germicide and a strong bleaching agent. Sulfur dioxide is employed as a *refrigerant* and is occasionally responsible for poisoning. The gas is a powerful irritant of the respiratory passages and the symptoms and treatment of poisoning are the same as for the lung irritants described under the war gases. Sulfur dioxide is irritating in a concentration of 0.001 per cent, and ten times this concentration borders on the lethal.

Ichthammol

Ichthammol (*Ammonium Ichthosulfonate*), N.F., B.P. (Ichthyol), is the product obtained from sulfonating and neutralizing with ammonia the distillate of certain bituminous schists. The resulting compound contains approximately 10 per cent sulfur in the form of organic sulfonates. It is a brown, viscous fluid with a strong characteristic odor and is soluble in both aqueous and organic solvents. Ichthammol is demulcent, emollient and somewhat antiseptic. It is used alone, or in combination with other antiseptics, for the treatment of skin disorders such as *erysipelas, psoriasis* and *lupus erythema-*

tosus and to promote healing in chronic inflammations. The drug is commonly employed in the form of *Ointment of Ichthammol,* N.F., which contains 10 per cent in a base of petrolatum. The drug was at one time widely employed, but has lost much of its popularity.

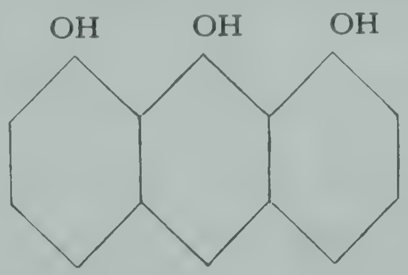
Chrysarobin

Chrysarobin, U.S.P., B.P., is a mixture of the neutral principles obtained from *Goa powder,* a substance deposited in the wood of *Vouacapoua Araroba,* a tree indigenous to India and Brazil. It consists of an orange-yellow powder, insoluble in water, but more soluble in a variety of organic solvents. The neutral principles, chief of which is *chrysophanolanthranol,* are irritants and possess fungicidal properties. When taken orally, chrysarobin causes gastro-intestinal irritation, vomiting and diarrhea. That portion which is absorbed may irritate the kidneys sufficiently to cause the appearance of albumin, red blood cells and casts in the urine. On the skin, the drug causes marked irritation unless it is suitably diluted.

Official ointments of chrysarobin are *Chrysarobin Ointment,* U.S.P. (six per cent), B.P. (four per cent). The ointments stain skin and clothing a brownish-violet color. The drug in ointment form is employed in the treatment of *ringworm infections, psoriasis* and other *skin disorders.* In the treatment of psoriasis, chrysarobin is one of the most effective of available agents. The concentration of the drug may have to be increased many times over that of the official ointment before satisfactory results are obtained. Some of the neutral principles may be absorbed through the skin and excreted into the urine, partially unchanged and partially oxidized to chrysophanic acid. The latter compound colors an alkaline urine red. The unchanged chrysarobin may irritate the kidney in the course of its excretion.

Dioxyanthranol. Dioxyanthranol is a synthetic compound which differs from the chief active ingredient of chrysarobin only by the lack of a methyl group. The drug has been widely employed in Europe since 1916 but was not extensively studied in the United States until investigated by Beerman and associates (1935). Dioxyanthranol occurs as a yellow crystalline powder, insoluble in water but soluble in organic solvents. The advantages it possesses over chrysarobin are that (1) it is a synthetic chemical of exact composition which can be cheaply prepared, (2) it is effective in low concentrations, (3) it is less irritant to the skin and kidneys, and (4) it causes comparatively little discoloration of clothes or skin. The compound is probably just as effective as chrysarobin in the treatment of *psoriasis, mycoses* and other cutaneous disorders. It has also proved of value in the treatment of *alopecia areata,* but Goodman (1939) warns against the prolonged use of the drug in that exhaustion of the pigment-producing power and further loss of hair may occur.

Dioxyanthranol has the following structural formula:



Dioxyanthranol

It is marketed under the name *Anthralin,* and is available in ointment form in concentrations of 0.1, 0.25 and 0.5 per cent. The weakest preparation is first employed and the strength is then increased according to the tolerance of the patient. The Council (1935) reviewed the status of dioxyanthranol and approved of the non-proprietary designation "anthralin"; but the compound has not been accepted for inclusion in N.N.R., awaiting further studies on its pharmacology and clinical efficacy.

Beta-Naphthol

The chemistry, general pharmacology, preparations and use of beta-naphthol as an anthelmintic are discussed elsewhere (page 887). The drug also possesses significant germicidal and fungicidal actions. Beta-naphthol is more germicidal than phenol, but is used more extensively as a parasiticide. It is usually employed in an ointment base in a concentration of five or ten per cent for the treatment of *ringworm, psoriasis* and *pediculosis.*

BALSAMS

Balsams consist of naturally occurring mixtures of resins, volatile oils and organic acids. They are employed to a limited degree in the dressing of wounds for their stimulant and mild antiseptic action. They also act as mild parasiticides. In addition, they are used in inhalant mixtures as expectorants. There are a number of balsams, and traditionally each has rather specific uses.

Peruvian Balsam, U.S.P., B.P., consists of a dark brown viscid liquid. It is used in full strength or diluted with a vegetable oil as a dressing for wounds and in the treatment of such conditions as epidermophytosis and pediculosis. *Balsam of Tolu,* U.S.P., B.P., is a yellowish-brown plastic solid. It was formerly used internally as an expectorant. *Syrup of Tolu,* U.S.P., B.P., is rather widely employed as a vehicle for expectorant drugs, but has no specific virtue for this purpose. *Benzoin,* U.S.P., is a balsam which is sometimes used as an inhalant expectorant in the form of the official tincture or compound tincture; but benzoin finds its chief application as a component of *Benzoinated Lard,* U.S.P., B. P., a common ointment base. The benzoin is added to prevent rancidity. *Styrax,* U.S.P., B.P., a sticky, gray, opaque, semisolid mass, is sometimes employed as a parasiticide in the treatment of skin infections. It is used diluted with an equal part of an inert vegetable oil. *Copaiba* (*Balsam of Copaiba*), U.S.P., B.P., is a yellow viscid liquid which formerly was rather widely employed as a urinary antiseptic, especially in the treatment of gonorrhea. With the advent of much more effective agents, the drug has become obsolete.

Volatile Oils

A number of volatile oils have been employed in the past for the treatment of urogenital infections, especially gonorrhea. The oils are taken orally and in the course of their excretion exert a slight antiseptic action in the urinary tract. They are much inferior to the modern urinary antiseptics and are now seldom employed. *Oil of Santal* (*Sandalwood Oil*), U.S.P. (*Oil of Sandal Wood,* B.P.), is one that is still official. It consists of a pale yellow, viscid, oily liquid obtained from the dried heartwood of *Santalum album.* Two other volatile oils in this category are *oil of copaiba* and *oil of cubebs.*

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CHAPTER 49

DRUGS USED IN THE CHEMOTHERAPY OF HELMINTHIASIS

Anthelmintics are drugs used to rid the body of a specific group of parasitic worms known as helminths. The great importance of this class of drugs lies in the fact that helminthiasis is the most common disease in the world. Approximately 800 million people are hosts to various types of worms.

The term *anthelmintic* is commonly used to designate locally acting drugs employed to drive worms from the *gastro-intestinal tract.* There are several types of worms which penetrate *tissue* and the drugs used to combat them should also be classified under the general term of anthelmintics. The anthelmintic drugs are occasionally subdivided into vermicides and vermifuges, depending upon whether the agent actually kills the parasite or merely removes it from the host. This arbitrary division can well be abandoned because the anthelmintics manifest both actions, depending upon the dose used. The anthelmintics may therefore broadly be defined as drugs used to combat any type of helminthiasis.

Worms parasitic for man belong to widely different zoological species and vary with respect to structure, physiology, and habitat in the human host. Consequently, before therapy can be instituted, it is necessary to identify the particular worm with which one is dealing. This requires a comprehensive knowledge of the common types of worms which are parasitic in man and their susceptibility to chemical agents before therapy can be placed upon a rational basis.

Classification of Helminths. The worms which are parasitic to man can be divided into two main groups, the Platyhelminthes (cestodes and trematodes) and the Nemathelminthes (nematodes). The platyhelminthes may be subdivided into the *tapeworms* and *flukes.* The tapeworms are flattened segmented worms. They have no body cavity and absorb their nutriment through the surface of their body which is soft in nature and has no resistant cuticle. The flukes are nonsegmented, contain a digestive tract with a single oral opening, and also have a soft body surface. Both the flukes and the tapeworms with few exceptions are hermaphroditic. Nemathelminthes are round in cross section. Their body surface is protected by a relatively impermeable cuticle. They possess a simple straight digestive tract with both oral and anal openings and they are bisexual.

Following is a classification of the most important of the helminths causing infestation in man.

I. Nemathelminthes (Nematodes)

Ancylostoma duodenale	hookworm
Necator americanus	
Ascaris lumbricoides	(roundworm)

Trichocephalus trichiuris............... (whipworm)
Strongyloides stercoralis
Oxyuris vermicularis...................(pinworm)
Trichinella spiralis
Filaria bancrofti

II. Platyhelminthes

A. *Tapeworms (cestodes)*
  Hymenolepis nana...................(dwarf tapeworm)
  Taenia saginata.....................(beef tapeworm)
  Taenia solium.......................(pork tapeworm)
  Diphyllobothrium latum.............(fish tapeworm)
B. *Flukes (trematodes)*
  Schistosoma haematobium, mansoni,
    or japonicum
  Paragonimus westermanni
  Clonorchis sinensis
  Fasciolopsis buski
  Heterophyes heterophyes
  Metagonimus yokogawai
  Gastrodiscoides hominis

Dangers of Parasitic Infestation. Worms are deleterious to their host for a number of reasons. (1) They may rob the host of food, one of the least important of their noxious effects. The lay opinion that an increase in appetite is evidence of worm infestation is apparently unsubstantiated by clinical data. (2) Worms may cause mechanical injury to organs or they may obstruct ducts. These effects are often serious. For example, hookworms can do extensive damage to the intestinal wall with resulting serious blood loss to the host. Lung flukes can burrow into and injure pulmonary tissue. The eggs of the schistosoma or blood flukes are injurious to the capillaries. Liver flukes may obstruct the bile ducts and filariae may block the lymphatics. Even such a relatively innocuous parasite as the ascaris may be present in the intestine in such large numbers as to cause obstruction. (3) The host may absorb toxic substances produced by the parasite. (4) The traumatizing action of the worm may provide a portal of entry for other organisms, especially bacteria.

It is desirable, therefore, even though a patient may be symptom-free, to get rid of parasites as soon as it has been established that they are present. At the same time it must be remembered that most of the anthelmintic drugs are toxic, and their use should be limited to cases in which the diagnosis of parasitic infestation has been made by actual identification of the causative worm.

Properties Desirable in Anthelmintics. Because anthelmintics are toxic to the host as well as to the parasite, a primary consideration in their choice is the *therapeutic index*. That agent which is most toxic for the worm and has minimal effects on the patient is obviously the most desirable. Anthelmintics vary widely in their therapeutic indices. Many of the drugs used today are therapeutic inheritances and are highly toxic. In contrast, a number of new synthetic drugs are rapidly displacing the older empirical agents. They have proved to be safe and clinically effective and are the anthelmintics of choice. Another important consideration in the selection of an anthelmintic is its *cost*. Many patients with helminthiasis are impoverished individuals who must be treated in free clinics. Some of the older anthelmintics are the most expensive of all medicines. *Ease of administration* is also a factor, and a drug that is pleasant to take and causes a minimum of side-effects is much to be desired.

ASPIDIUM (MALE FERN)

Crude preparations of this drug were known to the ancients and Pliny and Galen used male fern as an anthelmintic.

Source and Preparations. Varieties of aspidium plants are common throughout the world. The species from which the official drug is obtained, *Dryopteris filix mas,* is a common fern in Great Britain. The underground stems or rhizomes of this plant are collected in Autumn, dried and then extracted.

The active principles of aspidium are various non-nitrogenous acids of which *filicic acid* is the most important. Filicic acid is a phloroglucin derivative and it is interesting to note that various other plants which have been adopted empirically as anthelmintic agents in widely separated portions of the world contain active principles of a similar chemical nature.

The official U.S.P. preparation is *Oleoresin of Aspidium* (*Extract of Male Fern,* B.P.), an ether extract of the dried rhizomes. It is a thick, dark green liquid.

Pharmacological Actions. *Gastro-intestinal Tract.* Aspidium is a strong *local irritant.* When given undiluted, it causes nausea, vomiting and bloody diarrhea. In advanced pregnancy, reflex uterine stimulation may result in abortion.

Central Nervous System. In high doses, aspidium stimulates the spinal cord. Muscle tremors occur and may proceed to tonic convulsions. Stimulation is followed by an ascending depression until finally the medulla is affected and respiration fails. The drug also has a special affinity for the optic nerve and may cause blindness.

Circulation. Aspidium is a direct cardiac depressant and large doses slow the rate and weaken the force of contraction.

Smooth Muscle. Smooth muscle is markedly depressed by aspidium, and this is probably the basic mechanism of its anthelmintic action. The drug paralyzes the muscle of the parasite, and allows the worm to be removed from the intestinal tract by a cathartic.

Absorption and Excretion. Aspidium is a locally acting anthelmintic and therefore it is desirable to keep the drug in the intestinal tract and limit its absorption as much as possible. This not only allows a high concentration at the site of action but also reduces the possibility of systemic poisoning. Nevertheless some aspidium is absorbed and this portion is excreted in the urine, partially unchanged and partially decomposed. The drug is irritating to the kidney. Its excretion is accompanied by an unidentified reducing substance in the urine.

Toxic Symptoms. Unfortunately, there is little relationship between the dose of aspidium administered and the toxic symptoms which may follow. Variation in individual susceptibility and degree of drug absorption probably accounts for this fact. At times, therefore, therapeutic doses will cause very uncomfortable or even dangerous symptoms. The mild symptoms of poisoning are headache, vertigo and an increase in reflex excitability. Slight jaundice may also be noted. More severe intoxication is characterized by gastro-enteritis with abdominal pain, nausea, vomiting and bloody diarrhea. Vision is also affected and there may occur xanthopsia, amblyopia, or temporary blindness. In very severe cases, the victim suffers from muscle cramps which are soon followed by tonic convulsions. Consciousness is lost, respiration is depressed and death may result either from respiratory or cardiac failure. If the patient recovers from these severe symptoms, permanent unilateral or bilateral blindness is not uncommon.

Treatment. The treatment of poisoning is mainly symptomatic. A saline cathartic should be given to remove the drug from the intestinal tract. Convulsions can be controlled by the intravenous use of soluble barbiturates. The respiration should be stimulated if necessary.

Indications. Aspidium is a useful drug for ridding the intestinal tract of tapeworms. It is especially effective against *Taenia* and *Diphyllobothrium.*

Contraindications. The drug is useless against helminths other than tapeworms. It should not be employed in weak or emaciated individuals, in persons with gastro-intestinal ulceration, in those suffering from diseases involving the heart, liver or kidney, or in pregnant women. Also it is a dangerous drug to give to children. If unsuccessful, aspidium should not be repeated until a rest period of at least seven to ten days has intervened.

Technic of Administration. The patient should be placed on a fat-free diet for two days prior to the administration of aspidium. Lunch and supper are omitted on the previous day but fluids may be taken liberally. A cathartic of magnesium sulfate is given the evening before. The following morning, aspidium is given in two divided doses, one hour apart. The total dose for an adult is five grams, and for a child, 0.5 gram per year of age, the total dose not to exceed five grams. The drug has a most unpleasant taste and should be prescribed in capsules or in a suitably flavored vehicle. Two hours after the second dose, the patient again receives magnesium sulfate. This serves the purpose of ridding the intestine of both the parasite and the toxic anthelmintic. When the worm is dislodged, the head may break off and remain in the intestinal tract. For this reason, a generous soapsuds enema is given two hours after the second saline cathartic. All of the stools passed should be strained and carefully examined. The identification of the head of the worm is the only assurance that therapy has been successful.

An important feature of the above procedure is the use of *saline* cathartics. An oily drug such as castor oil is to be avoided because it will promote the absorption of the toxic aspidium. It is for this reason, also, that fats are excluded from the diet. The purpose of the preliminary fast and cathartic is to reduce to a minimum the intestinal contents and thus allow maximal contact between the anthelmintic and the parasite.

KOUSSO (CUSSO)

This drug is mentioned because its active principle, kosotoxin, is chemically related to the active constituent of aspidium, both being derivatives of phloroglucin. Kousso is obtained from the female flowers of *Hygenia abyssinica,* a plant found in Abyssinia. It is similar in action to aspidium but is less active and less toxic. An infusion of Kousso is official in the B.P. but not in the U.S.P. It is effective against the same helminths as aspidium, is used in the same manner, and is sometimes employed in combination with aspidium.

PELLETIERINE

Pelletierine is obtained from the bark of the pomegranate tree, *Punica granatum.* The tree is indigenous to India where, for centuries, its bark has been employed as an anthelmintic. The drug was first introduced into Europe in 1805.

Active Constituents and Preparations. The active constituents of pomegranate bark consist of several alkaloids, the most important of which is pelletierine ($C_8H_{15}NO$), named after the famous French chemist Pelletier who first isolated the compound. The drug is usually prescribed as *Pelletierine Tannate* (U.S.P., B.P.). This preparation is not a pure alkaloid but is a mixture of the tannate salts of the several alkaloids of the bark. It consists of a light yellow, odorless, amorphous powder with an astringent taste. It is soluble in alcohol, and to the extent of 1:250 in water.

Pharmacological Actions. Pelletierine has a marked action on the nervous system, both central and peripheral, and on voluntary muscle. The drug first stimulates and then depresses the central nervous system. It also has a selective toxic action on the optic nerve. The action on skeletal muscle is similar to that of veratrine, in that it impedes the relaxation following contraction. Pelletierine also has a curare-like action and thus paralyzes voluntary muscle.

Toxic Symptoms. Dizziness is a common complaint even after a therapeutic dose of pelletierine. In cases of more severe poisoning, nausea, vomiting and diarrhea are frequent. Reflexes are hyperactive at first but soon muscular weakness ensues. At this time muscle twitching and cramps are common. Mydriasis and visual disturbances are also noted. Paralysis eventually develops and this may involve the respiratory muscles and cause death.

Treatment. The drug should be removed by the use of a saline cathartic. Subsequent treatment is purely symptomatic. The respiration fails due to muscular paralysis and therefore central respiratory stimulants are not effective. Artificial respiration must be instituted.

Indications. The drug is especially effective against *Taenia solium.* It is ineffective against *Hymenolepis nana.*

Contraindications. These are much the same as for aspidium. The toxic nature of the drug prohibits its use in all but robust adults.

Dosage and Technic of Administration. The patient should be prepared in the same manner as for aspidium. The drug is usually given in a single dose of 0.25 gram of the tannate. This is followed by a cathartic within 30 minutes.

OIL OF CHENOPODIUM (AMERICAN WORMSEED)

Oil of chenopodium is obtained from *Chenopodium ambrosioides,* a plant commonly known as the Jerusalem oak. It is indigenous in the Southern portions of North America and was used as an anthelmintic by the American Indians.

Active Constituent and Preparations. The active drug is an oil containing a mixture of volatile substances. The active constituent is *ascaridol,* an organic peroxide with the empirical formula $C_{10}H_{16}O_2$. The oil, as obtained from the plant, varies in its content of ascaridol and therefore in its activity. The U.S.P. specifies that medicinal preparations of the oil contain not less than 60 and not more than 80 per cent of an acetic acid soluble fraction, which is mainly ascaridol (B.P.—not less than 65 per cent ascaridol). This mixture is the official preparation of the drug. Ascaridol is obtainable in pure form but its cost is prohibitive. *Oil of Chenopodium* (*Oil of American Wormseed*), U.S.P., B.P., is a colorless or pale yellow liquid having a characteristic unpleasant odor and a bitter burning taste. It is soluble in 70 per cent alcohol, to the extent of 1:8.

Pharmacological Actions. *Local.* Oil of chenopodium is a local irritant. When applied directly to the skin it acts as a rubefacient. It is also toxic to protozoa and was once used in the treatment of amebic dysentery.

Gastro-intestinal Tract. Oil of chenopodium is very irritant to the gastro-intestinal tract. The oil has a burning taste, stimulates salivary flow and reflexly stimulates gastric secretion. In high doses, the drug is sufficiently irritating to produce vomiting. It is depressant to the smooth muscle of the bowel and may cause constipation which should be counteracted by the use of a cathartic. The anthelmintic action apparently results from the depression of the musculature of the parasite.

Central Nervous System. The drug first briefly stimulates and then depresses the central nervous system. The depressant action is sufficiently pronounced to produce unconsciousness. The medullary centers are also affected, especially the vasomotor center. In addition, chenopodium affects the special senses, and both sight and hearing are impaired.

Circulation. Following large amounts of oil of chenopodium, the blood pressure falls as the combined result of depression of the vasomotor center and a direct depressant action on cardiac muscle.

Absorption, Fate and Excretion. Absorption occurs readily from the intestine. The oil is partially excreted by the lungs and its pungent odor can be detected on the breath. The remainder is apparently destroyed in the body for it cannot be detected in other channels of excretion.

Toxic Symptoms. Large therapeutic doses may cause nausea, vomiting, tinnitus and impaired vision. After toxic amounts, there is profound depression followed by unconsciousness. The respiration is slow and occasionally convulsions may occur. The drug is also toxic to the kidney and liver, and hematuria, albuminuria and jaundice may be observed.

Treatment. The unabsorbed drug should be hastened along the intestine by a saline cathartic. Treatment is symptomatic and consists for the most part in combating the circulatory and central nervous system depression. The kidneys should be protected from irritating concentrations of the drug by the administration of copious amounts of fluid.

Indications. Oil of chenopodium is useful in ridding the intestines of nematodes. *Hookworm* and *ascaris* are the helminths most vulnerable to this drug. It is also effective against dwarf tapeworm. Due to its toxic actions, however, it has largely been replaced by less noxious but equally effective preparations.

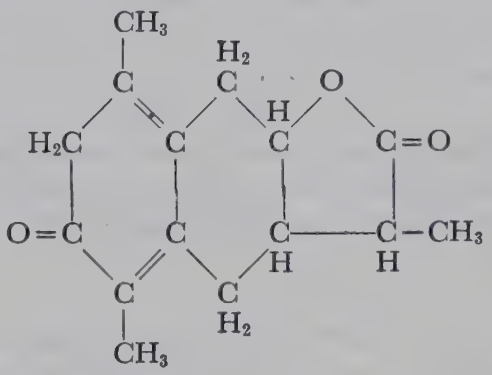
Contraindications. Oil of chenopodium should not be used in patients with renal, cardiac or hepatic disease. Neither should it be given to individuals with gastro-intestinal ulceration. Great caution should accompany the administration of this drug to children.

Dosage and Technic of Administration. The usual dose of oil of chenopodium is 1.5 to 3.0 cc. This is divided into three portions and administered in hard gelatin capsules at hourly intervals. A cathartic of magnesium sulfate is given one hour after the last dose of drug. The patient should neither be fasted nor receive a purge prior to oil of chenopodium since such a procedure seemingly retards rather than enhances the action of the drug. It is also best to prescribe a high carbohydrate diet for a few days beforehand in order to augment the liver glycogen reserve and thus diminish toxicity for the liver.

SANTONIN

Santonin is one of the oldest anthelmintic drugs, and was extensively employed by the early Greeks and Romans. It is obtained from various species of *Artemisia* plants (Levant wormwood) which are widely distributed. For a long time, the main supply of the drug was from Russia where the species *Artemisia maritima,* rich in santonin, grows in profusion, but other sources of this drug have been developed.

Active Constituents and Preparations. Santonin is obtained from the plant as a chemically pure crystalline substance. The active ingredient is an inner anhydride of santonic acid, a naphthalene derivative, which has the following structural formula:



Santonin

The official preparation is known as *Santonin,* U.S.P., B.P. The drug is most conveniently administered in capsules. It consists of odorless, colorless crystals having a slightly bitter after-taste. It is insoluble in water and soluble 1:43 in alcohol.

Pharmacological Actions. *Local.* Santonin is non-irritating and tasteless. For these reasons, it is one of the simplest of the anthelmintics to administer.

Central Nervous System. In low doses, the only effect of santonin is on the special senses. Color vision is especially disturbed. There may also be changes in the sense of hearing and occasionally of smell and taste. Large doses of santonin stimulate the central nervous system, and epileptiform convulsions occur in man. Severe depression follows.

Circulation. The circulation is affected only by toxic doses of the drug which cause some degree of cardiac depression.

Anthelmintic Action. Santonin is mainly effective against roundworms. These are expelled alive and active. It is therefore believed that santonin is not directly toxic to the parasites. Rather the worms are irritated by the drug and migrate from the small intestine to the colon from whence they are eliminated.

Absorption, Fate and Excretion. Santonin is fairly soluble and readily absorbed in the intestine due to the alkaline reaction and solvent effect of the bile salts. This rapid absorption may lead to toxic reactions. The drug is excreted as a highly pigmented substance of unknown composition. This excretory product colors acid urine a deep yellow and alkaline urine pink. Santonin is irritating to the kidneys and hematuria is sometimes observed after large doses.

Toxic Symptoms. The amount of santonin absorbed from the intestine is so variable that even with therapeutic doses disturbances in vision may occur. Objects first appear blue, but soon xanthopsia develops and bright objects then appear yellow. In addition, headache, vomiting and confusion are not uncommon. With greater absorption or after larger doses, poisoning may be severe. Abdominal pain and diarrhea sometimes occur. The skin is cold and covered with perspiration. There is a marked fall in body temperature and a skin rash may develop. Soon muscle tremors appear and progress to epileptiform convulsions. The heart and respiration are depressed. The urine may be bloody as a result of renal irritation.

Treatment. The drug should be removed by stomach tube and catharsis. If convulsions have set in, they should be controlled by the intravenous use of short-acting barbiturates. Symptomatic and supportive therapy should also be instituted with special attention to the circulation and respiration.

Indications. Santonin is most effective against ascaris infestation.

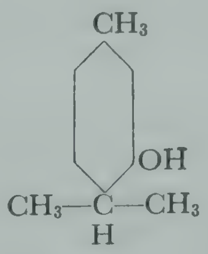
Contraindications. There are no specific contraindications to this drug but it should be employed cautiously and under strict medical supervision.

Dosage and Technic of Administration. The dose of santonin for adults is 0.06 to 0.20 gram; for children, 0.01 gram per year of age. This amount is given once daily for two or three consecutive days. The anthelmintic is accompanied by a cathartic, traditionally calomel, because it is believed that santonin acts more powerfully in the presence of bile and for a long time calomel was erroneously thought to be a choleretic. It is perhaps best to give a more dependable cathartic, such as magnesium sulfate. If calomel is used, it should be followed by a saline cathartic. Santonin should not be given on an empty stomach for this enhances its absorption, and fats should be excluded from the diet.

THYMOL

Thymol was extensively employed in the past for the treatment of hookworm infestation but now has largely been replaced by less toxic but equally efficient drugs. Nevertheless thymol is still used and there are some authorities who think highly of it.

Source, Chemistry and Preparations. Thymol belongs to a group of chemicals known as stearoptenes. It is contained in the essential oil of many plants, the most common of which is *Thymus vulgaris*. This is a small evergreen shrub which is extensively cultivated. Thymol is methyl isopropyl phenol and has the following structural formula:



Thymol

The official preparation is *Thymol,* U.S.P., B.P., and consists of large, colorless crystals with a pungent aromatic odor. Thymol is soluble in water to the extent of 1:1000, and in alcohol 1:1.

Pharmacological Actions. *Local.* The local actions of thymol are similar to those of phenol. It is antiseptic in high dilutions and irritating to exposed tissue. Like phenol, it has a slight local anesthetic action.

Gastro-intestinal Tract. Thymol has a burning aromatic taste. After ingestion, it has a carminative action and imparts a feeling of warmth. The drug stimulates intestinal peristalsis and this may lead to evacuation of the bowels. In high concentration, it causes a superficial sloughing of the gastro-intestinal epithelium.

Central Nervous System. Like phenol, thymol is a central nervous system stimulant, but it is less prone to cause convulsions. It acts first on the higher centers. The stimulation is followed by depression and eventually by respiratory arrest.

Circulation. Thymol is very toxic to the heart. The force and amplitude of contraction of the perfused mammalian heart are depressed when the concentration of thymol is as low as 1:200,000. This is within the range of concentration attained in the blood after full therapeutic doses of thymol.

Absorption, Fate and Excretion. Most of the administered thymol is probably absorbed by the intestine. About one-half of the drug is destroyed in the body and the remainder is excreted in conjugated form as the sulfate or glycuronate. A small portion is oxidized to thymol hydroxyquinone which imparts a greenish tint to the urine. Upon standing, the color deepens until the urine appears almost black. Thymol is irritating to the kidneys and is likely to cause albuminuria and oliguria.

Toxic Symptoms. In many ways the toxic actions of thymol are related to those of phenol. The local effects of the drug, however, are not so severe. Nevertheless with large doses the patient experiences epigastric pain, nausea and vomiting. If large quantities are absorbed, there is evidence of central stimulation. The patient becomes talkative and confused. The face is flushed, the pulse rapid, and headache common. Roaring in the ears and temporary deafness are not infrequent. As poisoning proceeds, the patient lapses into unconsciousness. Convulsions rarely occur. Death may result from cardiac failure.

Treatment. Treatment is purely symptomatic. The drug should be removed in so far as possible (*see* phenol poisoning) and special attention given to the circulation and respiration.

Indications. Thymol is useful only against *hookworm.* The drug will kill this parasite in low concentrations, but has now largely been replaced by other anthelmintics.

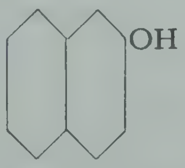
Contraindications. Thymol should not be given to debilitated individuals or those suffering from cardiac or renal disease.

Dosage and Technic of Administration. The total daily dose of thymol should not exceed 4.0 grams in men, or 3.0 grams in women and aged individuals. The dose in children varies from 0.2 to 2.0 grams depending upon age. A saline cathartic should be taken the night before and thymol therapy begun the next morning while fasting. The total dose of thymol is divided into two or three equal portions and taken at intervals of one or two hours. The last dose is followed by a saline cathartic. It is best not to repeat thymol medication for a week. The drug is most conveniently administered in gelatin capsules. It should be mixed with lactose because otherwise it tends to lump and escape solution in the bowel. The ingestion of alcohol and fats should be strictly avoided immediately prior to and during therapy.

BETANAPHTHOL

Betanaphthol was introduced in 1904 for the treatment of hookworm infestation. The drug enjoyed a brief period of popularity but has been almost completely replaced by safer and more efficient compounds.

Chemistry and Preparations. *Betanaphthol,* U.S.P., B.P., is a buff-colored powder obtained synthetically from naphthalene and has the following structural formula:



Betanaphthol

It is soluble 1:1000 in water and 1:0.8 in alcohol.

Pharmacological Actions. *Local.* Upon local application betanaphthol is a powerful irritant and corrosive. It is also germicidal and fungicidal, more so than phenol, and like the latter, it has some local anesthetic activity.

Gastro-intestinal Tract. The oral ingestion of betanaphthol causes a numbing of the tongue and a feeling of warmth in the stomach. It stimulates the musculature of the gastro-intestinal tract and in large doses the drug is very irritating, causing nausea, vomiting and diarrhea.

Central Nervous System. Betanaphthol first stimulates and then depresses the central nervous system. The stimulation is sufficient to result in convulsions. Depression of the respiratory center causes death when toxic amounts of the drug have been ingested. Betanaphthol also has a selective toxic action on the eye, causing retinal changes and opacity of the lens.

Circulation. Large doses of betanaphthol are depressant to the heart. In advanced poisoning, there is also central vasomotor depression and these two effects combine markedly to lower the blood pressure.

Absorption, Fate and Excretion. Betanaphthol is rapidly absorbed from the intestinal tract. After absorption, a portion is broken down but the remainder is excreted by the kidney, partly conjugated with glycuronic acid and partly oxidized to betanaphthoquinone, which gives the urine a dark red color. Betanaphthol is very toxic to the kidney and the urine is scanty and albuminous after large doses of this drug.

Toxic Symptoms. Therapeutic doses of betanaphthol are usually unaccompanied by toxic reactions. If this amount is exceeded or if absorption is exceptionally rapid, the symptoms of poisoning appear. These consist of abdominal pain, nausea, vomiting, diarrhea, and eventually central nervous stimulation, convulsions and terminal depression. The urine is dark, scanty and contains much albumin. The drug is toxic both to the kidney and liver and fatty degeneration of these organs can result. Betanaphthol is destructive to red blood cells. When given to malarial patients, the drug may cause hemolytic anemia.

Treatment. The treatment of betanaphthol poisoning is purely symptomatic. If large doses have been ingested, it is probable that gastric lavage with a vegetable oil would be advantageous in removing the drug, as is the case with phenol. A saline cathartic might also be used but the drug itself is sufficiently stimulating to the bowel to promote its own excretion. The circulation and the respiration should be supported. The administration of large amounts of glucose and saline solution would be protective for both the liver and kidney. Transfusion of blood may be needed for a severe hemolytic anemia.

Indications. Betanaphthol is effective against *hookworm,* but it should not be employed in view of the superior preparations which are available. Its use as a parasiticide and in the treatment of skin disorders is presented elsewhere.

Contraindications. Betanaphthol is especially dangerous to individuals with any liver or renal impairment.

Dosage and Technic of Administration. Betanaphthol has been given in oral doses as high as six grams but this is dangerous. If the drug is used, the amount should not exceed four grams, divided into two equal doses and followed by a saline purge. Some authorities recommend that a purge be administered before the drug is given. Others omit all cathartics and depend upon the irritant action of the anthelmintic itself to promote evacuation of the parasites.

CARBON TETRACHLORIDE

Carbon tetrachloride (CCl_4) is closely related chemically to chloroform ($CHCl_3$). The compound was first prepared in 1849 and was used as an anesthetic by Simpson, the discoverer of chloroform anesthesia. It was soon discarded, however, because of its high toxicity. The drug then disappeared as a therapeutic agent but remained prominent because of the poisoning it caused in industries where carbon tetrachloride is extensively employed as a solvent, especially for fats, oils, rubber and other organic materials. The chemical was reintroduced as a therapeutic agent by Hall (1921) who observed that it was 100 per cent effective in removing hookworms from dogs, and he recommended its use in human beings. Its value is now widely recognized and the drug is extensively employed as an anthelmintic.

Pharmacological Actions. *Local.* Like chloroform, carbon tetrachloride is a "general protoplasmic poison." When applied to the skin, it acts as an irritant and rubefacient. It is also irritating to mucous membranes.

Gastro-intestinal Tract. Taken orally, carbon tetrachloride has a pungent and burning taste, and produces a feeling of warmth in the stomach. It stimulates intestinal peristalsis by its irritant action.

Central Nervous System. The action of carbon tetrachloride on the central nervous system is exactly analogous to that of chloroform. It produces an irregularly descending depression, affecting first the higher centers, then the cord and lastly the medulla. When carbon tetrachloride vapors are inhaled, the drug is rapidly absorbed and its systemic action is prominent. After oral administration of the usual therapeutic dose, however, the concentration reaching the circulation is insufficient to produce systemic effects, and symptoms are rarely more serious than giddiness and slight drowsiness.

Circulation. Here again the actions of carbon tetrachloride and chloroform are similar. Carbon tetrachloride is toxic to the heart, being directly depressant to the cardiac muscle. This action coupled with central vasomotor depression may markedly lower the blood pressure if high concentrations gain access to the circulation.

Absorption, Fate and Excretion. Maximal absorption of carbon tetrachloride occurs when its vapors are inhaled. A concentration of one part of carbon tetrachloride vapor in 1000 parts of air is the upper limit that can be breathed with safety. The absorption and excretion of inhaled carbon tetrachloride follow the general rules for gases. After oral ingestion, intestinal absorption is limited, but there are factors which can markedly increase the amount of drug passing into the circulation. The duration of the intestinal sojourn is important because the compound is apparently absorbed at a constant, slow rate. Therefore a single dose which soon passes out of the bowel with minimal absorption is much less toxic than if the same amount were given in divided doses and more time were available for absorption. The intestinal contents also greatly influence the rate of absorption. If large amounts of fat are present, carbon tetrachloride is absorbed in this solvent through the lymphatics. Similarly, carbon tetrachloride is very soluble in alcohol which is freely absorbed. When carbon tetrachloride and alcohol are given simultaneously the toxicity of the former is greatly increased. Even after oral administration the drug is excreted in the expired air. That fraction which is unabsorbed appears in the feces dissolved in fats and fatty acids.

Toxicology. Carbon tetrachloride poisoning may be acute or chronic. Both types may arise from oral ingestion of the drug or inhalation of its vapors. Factors determining the form of intoxication are the amount of drug gaining access to the blood stream, the duration of exposure and the intervals between exposures. The predominant symptoms of *acute poisoning* are referable to the central nervous system. The patient first behaves as if inebriated. Convulsions are not uncommon. As absorption increases, progressive narcosis occurs. The oral ingestion of the drug in large amounts causes abdominal pain, nausea, vomiting, diarrhea and hiccough. Severe headache is also a frequent complaint. The action of carbon tetrachloride on the heart may lead to cardiovascular collapse.

If the patient recovers, he is still vulnerable to the *late toxic effects of acute poisoning.* Carbon tetrachloride has a specific toxicity for liver cells. Two types of pathological change result from this hepatotoxic action, namely, fatty degeneration and central necrosis. After a single exposure to carbon tetrachloride the maximal damage to the liver is observed at the end of 48 hours. If sufficient functioning tissue remains to sustain life, the damaged liver usually undergoes complete resolution and normal function returns.

The factors influencing the toxicity of carbon tetrachloride for the liver have been extensively investigated. A diet high in carbohydrate will definitely protect animals from toxic doses. It is believed by many that a liver rich in glycogen is less vulnerable to damage by a variety of hepatotoxic agents. On the other hand, it has been observed that a carbohydrate diet does not protect the liver from damage but rather exerts its beneficial influence by protecting the animal from toxic symptoms which accompany destruction of liver tissue. Calcium is also important in protecting against toxic effects of liver damage (Minot and Cutler, 1928; Minot, 1931; Cutler, 1932). After extensive destruction of liver tissue, guanidine accumulates in the blood due to faulty protein metabolism. Apparently guanidine is largely responsible for the toxic syndrome because many symptomatological features of hepatic destruction can be produced by intravenous administration of guanidine. Calcium is thought to detoxify guanidine in some unknown manner. Not only can calcium markedly protect an animal with extensive liver destruction but also it can protect against lethal doses of guanidine. As a result of these observations and similar evidence obtained from clinical cases of poisoning, high calcium diets are recommended in patients receiving carbon tetrachloride therapy. There is also evidence that a diet high in protein is effective in preventing injury from hepatotoxic agents (page 66).

In addition to the liver, the kidney is susceptible to carbon tetrachloride. Cloudy swelling, fatty infiltration and extensive tubular damage are not infrequent. (*See* review and case reports of Smetana, 1939.) There is some evidence that carbon tetrachloride is more toxic to the kidney when liver function is abnormal, as for example, in patients with hepatic cirrhosis.

Subacute or chronic carbon tetrachloride poisoning results from repeated exposure to the drug. It is usually encountered in industry but can result from improper medication. The liver is the chief site of injury and cirrhosis may occur. Experimentally, chronic hepatic cirrhosis can be readily produced by repeated exposure (Stasney and Higgins, 1936). In addition to liver damage, a severe macrocytic hyperchromic anemia may develop. This anemia differs from pernicious anemia and is due in part to liver damage and in part perhaps to a direct action of the chemical upon the bone marrow. In industrial poisoning, severe dermatitis, bronchitis, and conjunctivitis result from exposure to carbon tetrachloride fumes.

Treatment. After oral ingestion of the drug, the stomach should be washed and a saline cathartic administered to hasten elimination, because the extent of intestinal absorption is a function of time. The remainder of the treatment is symptomatic. Special attention should be given to the heart and respiration. In order to avoid in so far as possible the late toxic symptoms of acute poisoning, the patient should be given large amounts of glucose and a diet high in carbohydrates and calcium.

Indications. Carbon tetrachloride is of value chiefly in the treatment of *hookworm infestation.* It is probably one of the most efficient drugs for this disease but has the disadvantage of being toxic. It is very cheap, however, a single dose costing less than one cent, and in the mass treatment of hookworm infested populations expense is an important consideration.

Contraindications. Carbon tetrachloride should not be given to individuals suffering from diseases of the liver, kidneys, heart or lungs. It is also contraindicated in alcoholics, emaciated individuals, or those suffering from calcium deficiency. In a patient with combined hookworm and ascaris infestation, carbon tetrachloride is dangerous unless accompanied by an ascaricide.

Preparation. *Carbon Tetrachloride,* U.S.P., B.P., is a volatile, colorless liquid which has an odor similar to chloroform and a burning taste. It is soluble 1:2000 in water and miscible with organic solvents.

Dosage, Technic of Administration and Precautions. The average dose of carbon tetrachloride for children is 0.2 cc per year of age. The adult dose is three cc. If possible, the diet before the administration of the drug should be high in carbohydrate and calcium and low in fat. The patient should be instructed to eat a light meal the previous evening. The next morning the carbon tetrachloride is taken on an empty stomach. It is conveniently given in hard gelatin capsules, but care must be taken not to break them in the mouth or high concentrations of the vapor may be inhaled. Two hours later, a saline cathartic is administered. Some authorities recommend that the drug be taken emulsified in skimmed milk.

Oil of chenopodium has been combined with carbon tetrachloride when an ascaris infection accompanies hookworm, the former drug acting on both parasites. The schedule is exactly as described except that the dose of carbon tetrachloride is reduced to 2.2 cc and to this is added 0.8 cc of oil of chenopodium. Hexylresorcinol is a better agent to use in patients with this combined infestation.

Carbon tetrachloride succeeds in removing more than 90 per cent of the hookworms from the intestinal tract. If the results are not favorable after the first administration, a second dose may be given, but *only after a rest period of three weeks.* If this is then not successful, another drug should be chosen rather than risk a third trial.

TETRACHLORETHYLENE

Tetrachlorethylene is a drug which promises to replace carbon tetrachloride as an anthelmintic. It is an unsaturated halogenated hydrocarbon of the following structural formula: $Cl_2:C = C:Cl_2$. Its physical properties are much like those of carbon tetrachloride. The drug, however, is only one-fifth as soluble in water and in the absence of fat in the intestines it is not absorbed to an appreciable extent. This probably accounts for its low toxicity for tetrachlorethylene has been administered orally daily to animals in high dosage with no indication of damage either to the liver or kidney. Also there have been no reports of toxic reactions in the clinical use of this drug. Furthermore, studies have failed to reveal an increase in blood guanidine or icteric index or a decrease in blood sugar or liver function. When one adds to these findings the fact that tetrachlorethylene is as efficient an anthelmintic as carbon tetrachloride, its true value can be appreciated.

Preparation. Tetrachlorethylene is official in the N.F. It is a colorless fluid having an ethereal odor, soluble 1:10,000 in water and miscible with organic solvents. It is conveniently taken in soft gelatin capsules, containing one cc each.

Dosage and Technic of Administration. These are exactly the same as for carbon tetrachloride. Patients may experience a slight dizziness after administration of tetrachlorethylene which indicates that some absorption must have taken place. However, there have been no reports of severe reactions.

Indications. Tetrachlorethylene is chiefly of value against *hookworm.* Therefore if a patient also harbors roundworms, medication should include an ascaricide. The drug is also of limited value against *oxyuriasis* (Wright and coworkers, 1937). The status of tetrachlorethylene as a vermifuge has been reviewed by the Council (1936).

HEXYLRESORCINOL

Hexylresorcinol is a well-known antiseptic. It was introduced into medicine as a urinary antiseptic by Leonard (1924) and was developed as an anthelmintic by Lamson and coworkers (1931).

Local Action. Hexylresorcinol is an efficient antiseptic when applied locally. It has a phenol coefficient of 45. Its solutions have a low surface tension and are odorless and stainless. It is quite irritating to tissue, however, and an occasional individual exhibits marked sensitivity to its local application (Walter, 1935).

Absorption, Fate and Excretion. After oral ingestion, about one-third of the hexylresorcinol is absorbed. The drug is excreted by the kidney and appears in the urine in a conjugated form which greatly impedes its action as a urinary antiseptic. The unabsorbed drug appears unchanged in the feces.

Toxicity. Hexylresorcinol is a local irritant, and damages tissue when applied in high concentration. Oral administration may lead to irritation of the mouth and gastro-intestinal tract. The systemic toxicity of the drug is low, probably because of its limited absorption. After a single therapeutic dose in man, hexylresorcinol causes no systemic disturbances. Repeated doses of this drug in dogs, however, may cause inflammation and necrosis of the small intestine and damage to the liver and heart.

Indications. Hexylresorcinol is perhaps the most valuble single anthelmintic agent. The drug is active against *hookworm, ascaris, oxyuris, dwarf tapeworm,* and *whipworm.* Although it may not be the most powerful anthelmintic, it has the advantage of low toxicity and thus can be repeated several times without danger or long rest periods. Its breadth of activity also permits its use in mixed infestations where other drugs which act only on one particular parasite might prove dangerous. Hexylresorcinol is particularly useful where contraindications to the more specific anthelmintics exist, as in debilitated individuals and children.

Preparation. Hexylresorcinol is a pale yellow, crystalline substance, $C_6H_3(OH)_2(C_6H_{13})$, having a slight pungent odor and an acrid astringent taste. It is soluble 1:2000 in water and freely soluble in organic solvents.

Technic of Administration and Dosage. These are the same regardless of the parasite being attacked. The drug is given in the morning on an empty stomach, the presence of food decreasing its effectiveness by combining with the drug. The dose for children below six years of age is 0.6 gram; for those from six to ten years of age, 0.8 gram; and for adults, 1.0 gram. The drug is most conveniently taken in hard gelatin capsules containing 0.2 gram each. Great care should be observed that these capsules are swallowed whole, for contact of the chemical with the oral mucous membrane may cause painful ulceration. Two hours later, a saline cathartic is given for the purpose of clearing the bowel of dead and dying worms. Food may be eaten after five hours have elapsed. The drug may be repeated at three day intervals.

GENTIAN VIOLET

The introduction of gentian violet as an anthelmintic in the United States by Faust (1930) was an important step in the treatment of helminthiasis for it marked the first moderately effective drug therapy against *Strongyloides stercoralis.* Later the dye was found to be the most effective anthelmintic for the treatment of oxyuriasis. The pharmacology of gentian violet is discussed under the antiseptics. The procedures used in the treatment of strongyloidiasis and oxyuriasis are outlined in the discussion of these parasitic diseases.

FICIN

Ficin is a proteolytic enzyme obtained from the sap of the *Ficus laurifolia*, a South American fig tree. For centuries this substance has been used by natives as an anthelmintic. The active ingredient is a ferment of the tryptic type (Robbins, 1930). The anthelmintic property of ficin is apparently the result of its proteolytic activity, the worms being digested by the drug. Experimental studies have shown that ficin is active against trichocephalus and oxyuris, two parasites that are resistant to therapy. It is also effective against hookworm, ascaris, and strongyloides.

The clinical use of ficin is limtied due to its unavailability. It has to be shipped long distances and is unstable. It has been reported that an Alabama fig tree yields a similar proteolytic enzyme which may deserve careful clinical investigation (Lamson, 1936).

The toxicity of ficin has been studied in dogs. The enzyme has no systemic effects, nor does it attack the healthy mucosa of the gastro-intestinal tract. However, if the intestine is irritated, ficin will attack the mucous membrane and cause erosion and hemorrhage. This may greatly limit the therapeutic usefulness of the drug.

ANTIMONY COMPOUNDS

Compounds of antimony are used in the treatment of parasitic diseases caused by various species of flukes. The pharmacology and toxicology of antimony and its compounds are discussed elsewhere. The specific use of antimony compounds in helminthiasis will be presented in the discussion of the treatment of certain worm infestations.

TREATMENT OF WORM INFESTATIONS

Round Worms

Hookworm: Necator Americanus, Ancylostoma Duodenale. These related species are commonly known as the *American hookworm* and the *Old World hookworm,* respectively. The parasites flourish in warm climates throughout the world. In the Western hemisphere, the common infesting organism is *Necator americanus,* also known as *Uncinaria americana,* and hookworm disease is often called uncinariasis. The life cycle and the symptoms produced by both parasites are so similar that they will be discussed together.

Hookworms are parasitic in the small intestine where they attach themselves to the mucosa and subsist by extracting blood from the host. The fertilized eggs pass out with the feces and incubate in moist soil. In an early stage of their larval development they become infective and regain entrance to their human host through the skin. They penetrate to the subcutaneous tissue, enter the venules and are carried to the lungs where they pass through the capillary walls to enter the alveoli. They then migrate up the bronchial tree to the epiglottis and from there into the alimentary tract, where they attach themselves to the villi and develop to maturity.

Symptoms. The symptoms produced by hookworm infestation can be divided into two groups, those caused by the larvae and those caused by the adult worms. The *larvae* produce a local reaction during their penetration of the skin. Symptoms consist of itching, burning, erythema, papular eruption and vesiculation at the sites of penetration, which are usually on the feet. The syndrome is popularly known as "ground itch." "Creeping eruption" is another type of skin disease caused by the larvae of *Ancylostoma braziliense,* a parasite of dogs and cats. Upon contact with human skin these larvae tunnel through the stratum germinativum at the rate of a few centimeters a day and cause an intense pruritus. Scratching often leads to infection. The larvae do not enter the circulation and merely produce local reactions.

The larvae of the human hookworm can produce changes in the lungs, which mainly consist of petechial hemorrhages where the larvae penetrate capillary walls. The symptoms seldom are severe and extensive pneumonitis is rarely encountered.

The adult hookworm is much more dangerous. It nourishes itself not on the intestinal contents but rather on the blood of the host. This results in varying degrees of anemia. While this blood loss is not a great one for the well-nourished individual, it must be remembered that hookworm infestation commonly occurs in the poorer economic classes, subsisting on poor diets inadequate in materials for hemoglobin regeneration. For some time it was debated whether the anemia of hookworm disease resulted from a simple blood loss or whether it was due to the action of some toxin liberated by the parasite. The question was further complicated by the fact that the anemia was often hyperchromic and macrocytic in type rather than that characteristic of blood loss. It is now fairly well agreed, however, that the anemia of hookworm disease is a secondary anemia of blood loss. If pernicious anemia occurs, the hookworm infestation is merely a precipitating and not a causal factor. The usual symptoms accompanying hookworm disease, those of a severe secondary anemia plus a general nutritional deficiency, are pallor, emaciation, weakness, dyspnea, indigestion and a hypoproteinemic edema.

Treatment. A dual problem usually exists in the treatment of hookworm disease. The first is to restore the blood level to normal and the second is to expel the intestinal parasites. Often it is necessary to improve the patient's general condition before it is safe to administer an anthelmintic. Proper diet and iron medication are usually quite effective in this regard but blood transfusion may occasionally be necessary.

There is a rather wide choice of anthelmintics available for treating hookworm disease. Some still consider *thymol* useful in this condition. *Carbon tetrachloride* has probably been used in more cases than any other preparation but it may cause toxic reactions. *Tetrachlorethylene* is now extensively employed. It is as efficient as carbon tetrachloride but much less toxic. The great disadvantage of the three drugs is that they are dangerous to use alone in the treatment of hookworm disease complicated with ascariasis. In such cases, the combination of carbon tetrachloride or tetrachlorethylene and oil of chenopodium is often employed, the last-named drug being effective against both roundworm and hookworm. *Hexylresorcinol* is gaining prominence in the treatment of hookworm infestation. It has the advantage of low toxicity and high efficacy against roundworms. A single dose of hexylresorcinol is capable of removing only about 75 per cent of the infesting organisms, but the drug can be given repeatedly at three day intervals. The doses and technic of administration of these anthelmintics have already been given.

Ground itch and creeping eruption may be treated with an ethyl chloride spray.

Ascaris Lumbricoides. *Ascaris lumbricoides,* known as the "roundworm," is cosmopolitan in distribution. Although cases of ascariasis are not infrequent in temperate climates, the parasite flourishes in warm localities. In the Southern United States the incidence of ascariasis is very high, especially in the children of poorer economic classes.

The worms, free and unattached, inhabit the small intestine. They are six to 14 inches long. The fertilized eggs are passed with the stool and incubate in soil to the embryonated form. When reingested, the shell is weakened by the digestive enzymes and motile larvae are liberated. These penetrate into the mesenteric venules and are carried to the lungs where they penetrate capillary walls to gain access to the alveoli. They then migrate up the bronchial tree, reach the epiglottis, are swallowed and once more gain access to the small intestine, where they finally develop to the adult form.

Symptoms. The symptoms of ascariasis may be divided into those caused by the migrating larvae and those resulting from the adult parasite. In the lungs, the larvae injure the capillary walls and cause petechial hemorrhages. If the pulmonary infestation is heavy the combination of leukocytic infiltration, epithelial débris, and serous exudate results in extensive consolidation. This condition has been termed "ascaris pneumonitis" and on occasions it may cause death. In very severe infestations, the larvae gain access to the systemic circulation, lodge in many tissues, and cause symptoms dependent upon the particular organs involved.

The adult worms in the intestinal tract are usually not dangerous. Their presence may cause abdominal discomfort and pain. Children harboring large numbers of parasites are likely to be undernourished and underdeveloped. *The real danger from the adult worms results from their migration.* This most often follows poor therapy. Under such circumstances the roundworms may block the lumen of the appendix and produce symptoms of appendicitis. They often occlude the common bile duct and occasionally invade the liver parenchyma. Perforation of the intestinal wall with subsequent peritonitis may rarely occur. If the worms are stirred to unusual activity, they may form a tangled mass and cause intestinal obstruction.

Treatment. The older, less efficient and more toxic ascaricides, although still extensively employed, are being slowly discarded. The two which still enjoy wide popularity are *santonin* and *oil of chenopodium.* An equally potent but far less toxic preparation is *hexylresorcinol.* A single dose of this agent is capable of removing an average of 95 per cent of the roundworms. When hexylresorcinol is properly administered a complete cure can be effected in 90 per cent of all cases. The technic of medication has already been described.

It should be borne in mind that poor therapy may cause migration of roundworms with unfortunate consequences. This may result from the wrong choice of drug, a mistake in the diagnosis of the infesting parasite, or from treatment of mixed infestations with a drug inactive against the roundworm. For example, it is not uncommon for an individual to harbor both roundworms and hookworms. If such a person receives carbon tetrachloride, the hookworms will be removed but the roundworms will only be irritated to migration or greater activity. If such a double infestation is suspected, either a drug active against both parasites or combined drug therapy should be used. Hexylresorcinol is a fortunate choice inasmuch as it is effective against both species.

There is no chemotherapeutic agent effective against the larval form of the roundworm.

Trichocephalus Trichiuris. *Trichocephalus trichiuris,* or whipworm, is encountered in the Orient and tropical countries. The adult parasite is usually found in the cecum, less commonly in the appendix and colon, and rarely in the lower ileum.

Symptoms. The symptoms caused by this parasite are mild. Rarely the worms may lodge in the appendix or may penetrate the bowel wall and give rise to peritonitis. Infested children may exhibit mild toxic symptoms and some degree of anemia.

Treatment. There is no known anthelmintic agent which is effective against this particular helminth but many are partially successful. *Oil of chenopodium* at times succeeds in ridding the host of the majority of the parasites. In the same category may be placed *carbon tetrachloride, tetrachlorethylene* and *hexylresorcinol.* Ficin may prove to be the most valuable agent against this helminth.

Strongyloides Stercoralis. *Strongyloides stercoralis* is commonly found in tropical regions and infestation with this worm is also frequent in the Southern United States.

The female worms, which are about two millimeters long, inhabit the duodenum and jejunum where they attach themselves to the intestinal wall and penetrate to the muscularis. Eggs are laid and hatch at the base of the villi. The larvae emerge into the intestinal lumen and are passed with the feces. In moist ground, they develop into adults, lay eggs which hatch, and the resulting larvae are independent of hosts. This free-living form of worm can continue through generations if conditions remain favorable. If conditions become unfavorable, however, the larvae metamorphose into a form which is infective for man. This larval form gains access to human beings by penetrating the skin or oral mucosa. The larvae reach the venous circulation and are carried to the lungs where they penetrate capillaries and enter alveoli. Here they develop to adolescent forms. Some of the females may imbed themselves in the pulmonary epithelium but the majority pass up the bronchial tree and down the esophagus into the intestinal tract. Here the females remain, but the males continue their migration and pass out of the body with the feces.

Strongyloides infestation may be self-perpetuating for not only can this organism enjoy an independent existence outside of the host, but also generations can succeed themselves within the host. This occurs when eggs hatched in the small intestine reach a stage of development which allows them to penetrate the intestinal wall and thus gain access to the circulation. There are cases of strongyloidiasis on record which have continued for fifteen years without the patient having had access to an external source of infection.

Symptoms. Symptoms vary in severity. Large numbers of parasites may cause only a feeling of abdominal discomfort. On the other hand, the organisms may be unsually destructive to tissue. The larvae, when they invade the skin or mucous membranes, produce a local reaction consisting of congestion, edema and intense pruritus. The passage of larvae through pulmonary capillaries may cause large areas of consolidation. If the larvae mature in the air passages, a chronic bronchitis may result. This species is also likely to damage intestinal epithelium more than any other parasite and to cause severe diarrhea and chronic enteritis.

Treatment. Gentian violet is one of the few chemotherapeutic agents effective in strongyloidiasis. The drug is usually administered before meals in enteric-coated capsules. The dose is 0.06 gram three times daily until a total of 3.3 grams has been given. In refractory cases, 25 cc of a one per cent solution of the dye may be introduced by tube directly into the duodenum. In late severe cases or when the parasites have invaded the lung tissue, gentian violet can be given by intravenous injection, 25 cc of a 0.5 per cent aqueous solution being injected very slowly. This injection is repeated every other day until not over five doses have been administered.

Simpson (1939) calls attention to the value of intraduodenal instillation of compound solution of iodine (four cc), given on alternate days until neither the duodenal contents nor feces show ova, parasites or larvae.

Oxyuris Vermicularis. *Oxyuris vermicularis* (*Enterobius vermicularis*), commonly known as pinworm or seatworm, is cosmopolitan in distribution. It usually infests the cecum and adjacent bowel.

The male is two to five and the female eight to 13 mm in length. The worms are attached by their heads to the mucosal wall. The gravid females lose their hold, migrate out of the anus, and crawl around the epidermal folds of the perianal and perineal regions. Here they soon dry out and die, but their embryonated eggs are scattered when the integument is ruptured. Both the worms and the eggs cause intense itching. Scratching results in reinfection by way of the hand and mouth. The eggs gain access to the gastro-intestinal tract where they hatch. The liberated larvae develop as they pass down the bowel and in the cecum they attain the adult form, become gravid and repeat the above cycle.

Symptoms. The systemic symptoms caused by this parasite are mild and often unnoted. The pruritus, however, is especially severe and irritating, and scratching may cause infection.

Treatment. Oxyuriasis has been treated with a variety of anthelmintic drugs, among which *gentian violet* has proven to be the most effective. The data of Wright and Brady (1940) and D'Antoni and Sawitz (1940) indicate that gentian violet is effective in 90 per cent of patients when properly administered. Wright and Brady recommend an adult dose of 64 mgm three times daily before meals. Children should receive 10 mgm a day for each year of apparent (not chronological) age in three divided doses. The drug is conveniently administered in the form of enteric-coated capsules. (*See* page 868 for preparations.) Gentian violet should be given in courses. A single course of 10 consecutive days duration seems to be as effective as more complicated routines of longer duration involving rest periods (Wright and Brady, 1940).

Untoward reactions of a mild nature accompany therapy with gentian violet and their incidence may be as high as 35 to 50 per cent. These consists mainly of nausea, vomiting, diarrhea and mild abdominal pain. An occasional patient may complain of headache, dizziness or lassitude. The reactions, which are probably due to the local action of the dye in the gastro-intestinal tract (for little absorption occurs), are usually encountered during the first few days of therapy. They may subside without the drug being discontinued, but in some instances it may be necessary to reduce the dosage or withhold treatment for a few days.

Gentian violet is contraindicated in the treatment of oxyuriasis complicated with ascariasis until after the ascarides have been removed. Other possible contraindications to the use of gentian violet listed by Wright and Brady are cardiac, hepatic or renal disease of an appreciable degree and disease of the gastro-intestinal tract. Abstinence from alcohol is recommended during the period of treatment.

Hexylresorcinol has also been employed in the treatment of oxyuriasis, although Wright and coworkers (1939) do not report very favorable results with the drug. It is given orally and by enema. The usual routine is to give a cleansing enema in the morning and an enema of 250 cc to 400 cc of a 0.1 per cent alkaline solution of hexylresorcinal in the evening. The medicated enema should be retained for 15 to 30 minutes. In addition, 1.0 gram of hexylresorcinol is given by mouth in the morning. This routine is repeated on three consecutive days.

Some success has attended the use of *tetrachlorethylene* in the treatment of oxyuriasis (Wright and associates, 1937), but the drugs already mentioned are probably much more effective.

Yellow oxide of mercury is of value in treating the cutaneous lesions around the anus. If all worms are killed locally, and superinfection is prevented, the infestation is self-limited.

Trichinella Spiralis. This parasite is cosmopolitan in distribution.

The adult worms are harbored in the intestinal tract where the females burrow deep into the mucosa to deposit eggs. The larvae gain access to the circulation and migrate to all parts of the body, but develop only in striated muscle where they become encysted. The muscles particularly involved are the diaphragmatic, laryngeal, lingual, orbital, abdominal and intercostal. The encysted larvae may remain viable for years. Man acquires this worm by eating the undercooked pork from infested swine.

Symptoms. During the period of invasion, nausea, vomiting, colic and watery diarrhea occur and last approximately one week. During the stage of migration of the larvae, the characteristic symptoms are muscular pains, myositis, localized edema and a remittent fever. There is often a marked leukocytosis characterized by a pronounced eosinophilia. Following encystment of the larvae there may be anemia and cachexia from the absorption of toxins and, in severe cases, delirium and somnolence.

Treatment. Trichiniasis is one of the few parasitic infestations which is apparently resistant to all known types of therapy. The common anthelmintics, organic arsenicals, antimony preparations, roentgen ray, radium, immune sera, etc., have been used without success. If the diagnosis is made while the parasites are still in the intestinal tract, thorough purging to reduce the number of harbored worms is advisable. The cathartic may be preceded by an anthelmintic such as tetrachlorethylene (Andes and associates, 1940). Therapy is otherwise purely symptomatic. Routine autopsy examinations indicate that approximately 18 per cent of the urban population of the United States are infested but few of these show symptoms (*see* review of Lewis and associates, 1940). A significant contribution to the chemotherapy of trichiniasis is nevertheless greatly to be desired. At present, prophylactic measures alone offer promise of reducing the incidence of infection. All pork should be thoroughly cooked before consumption. The encysted pork larvae are killed by exposure to 60 C. for five minutes.

Filaria Bancrofti. This parasite has failed to yield to chemotherapy. Filariasis is common in equatorial countries. In the United States there is a small region around Charleston, South Carolina, where the disease occurs. Man becomes infected with the larvae of this species from the bite of mosquitoes. The larvae migrate to the lymphatic system where they mature and liberate microfilariae. The most striking symptoms of filariasis are lymphangitis, adenitis and elephantiasis.

Treatment. The microfilariae can be killed with *organic arsenicals,* but no drug is known to be effective against the adult form of this parasite which is responsible for all the clinical symptoms of filariasis.

Tape Worms

Taenia Saginata. *Taenia saginata* or the beef tapeworm is the most common form of tapeworm. It is cosmopolitan in distribution.

Human infestation results from the ingestion of raw or partially cooked beef which contains the larvae of this organism. The adult worm is usually 10 to 15 meters in length and is harbored in the jejunum with the head imbedded in the mucosa and the body free in the intestinal tract. Successful therapy requires removal of this head.

Symptoms. The symptoms of infestation are not severe, and usually do not arise until the infesting organism has reached the adult stage. At this time diarrhea and weight loss may be observed, and an eosinophilic leukocytosis may occur. Diagnosis depends upon the identification of a gravid segment of the worm in the feces. Recognition of the isolated eggs can only establish the fact that one of the *Taenia* group is harbored in the intestine but will not distinguish between individual species.

Treatment. The drug of choice is *oleoresin of aspidium.* The technic of medication has already been described. At this point, however, it should be emphasized that one can only be assured of the success of therapy by identification of the head of the worm in the feces. Under the influence of an anthelmintic, the increased activity of the parasite will often result in the separation of the head and body segments, the head remaining imbedded in the intestinal mucosa. A complete new adult worm can be regenerated and the therapy has accomplished but little. Therefore all stools passed after the administration of the anthelmintic should be strained and carefully examined. If the head is not identified, a second course of the drug should be administered after a suitable rest period.

Taenia Solium. *Taenia solium* or the pork tapeworm is also cosmopolitan in distribution. It gains access to man as a result of the ingestion of insufficiently cooked pork infested with larvae known as pork "measle."

The worm which is approximately two feet in length is harbored in the upper two-fifths of the small intestine with the head burrowed in the mucosa. Usually only a single parasite is harbored, but the life span of such a worm may be as long as 25 years and therefore anthelmintic therapy is desirable.

Symptoms. The symptoms which result from harboring the adult form of the worm are not grave. They consist of slight indigestion, alternate diarrhea and constipation, anorexia and hyperesthesia. Rarely the head of the worm will penetrate the intestinal wall and peritonitis then results. A positive diagnosis can be made by identifying the gravid segments in the feces.

An attendant danger of *Taenia solium* infestation, and one that is unique to this type of tapeworm, is that of cysticercosis, the harboring of the cysticerci (larvae) in the tissues of the human host. This usually results from the ingestion of eggs of the parasite as a result of the contamination of the hands with feces, or the eggs liberated from a gravid segment may pass upward into the duodenum where they are digested. In either case the freed larvae gain access to the circulation and tissues in a manner exactly analogous to their cycle in the intermediate host, the pig. The seriousness of the symptoms which result depends upon the particular tissue invaded. The usual sites are the brain, orbit, muscles, liver and lungs.

Treatment. The drug of choice for ridding the host of the adult worm is again *oleoresin of aspidium.* The technic of administration has been described. In the case of infestation with *Taenia solium,* it is most important, however, that therapy be successful for there is a real danger that the patient may develop cysticercosis. Therefore if the head of the worm is not identified after the first administration of the drug, repeated courses at suitable intervals should be instituted. *Pelletierine tannate* is particularly effective against *Taenia solium* and this drug can be alternated with oleoresin of aspidium if the parasites prove to be resistant to expulsion, as they often are. The therapeutic procedure with pelletierine tannate has been outlined.

When treating a patient who is harboring *Taenia solium,* it is advisable to avoid, if possible, nausea and vomiting from gastric irritation by the use of enteric-coated capsules or direct instillation of the drug through a duodenal tube. Reverse peristalsis due to gastric irritation is very likely to carry the eggs of the parasite high in the duodenum and thus increase the danger of cysticercosis, for which there is no specific drug therapy.

Diphyllobothrium Latum. *Diphyllobothrium latum,* the fish tapeworm, is a common parasite in many European countries. In the United States infestation occurs particularly in the lake regions of Northern Minnesota and Michigan where certain fresh water fish, notably pike, harbor the larvae. The eating of inadequately cooked infested fish introduces the larvae into the human intestine where the adult worm may reach 30 feet in length.

Symptoms. These are essentially the same as those described for other types of tapeworms. For a time it was thought that infection with this particular helminth gave rise to a hyperchromic macrocytic anemia, called "bothriocephalus anemia." Most of these cases were observed in Finland, a country with a high incidence of both pernicious anemia and fish tapeworm disease. It is now believed that *Diphyllobothrium latum* infestation is only a precipitating factor when associated with pernicious anemia.

Treatment. Once again the drug of choice is *oleoresin of aspidium.* The technic of administration does not differ from that used against other forms of tapeworms. If the patient's symptoms are severe it is not improbable that more than one worm is being harbored. In such instances the identification of a single head is not a positive indication of successful therapy. If the total length of the segments recovered in the feces is over thirty feet it is likely that more than one worm was present in the bowel at the time therapy was instituted.

Hymenolepis Nana. *Hymenolepis nana,* the dwarf tapeworm, is cosmopolitan in distribution but infestation is more common in warm climates. It is the most frequent type of tapeworm disease in the Southern United States.

The life cycle of this helminth is unique in that no intermediate host is required, infection being transmitted from person to person. The adult worm which is only 25 to 40 mm in length is harbored in the ileum, the head burrowed in the mucosa.

Symptoms. Children are much more commonly infected than adults. If a large number of worms are harbored, the symptoms may be severe and include abdominal pain, diarrhea, insomnia, dizziness and epileptiform convulsions. Eosinophilia is frequently observed. Diagnosis depends upon identification of the eggs in the feces.

Treatment. Both *oleoresin of aspidium* and *oil of chenopodium* are effective against this parasite. However, as has already been mentioned, these drugs are too toxic to be given safely to children, in whom this helminth is more commonly found. Consequently *hexylresorcinol,* which is less effective but much less toxic, is the drug of choice for children. It is given on an empty stomach in a dose of 0.6 to 0.8 gram and is followed in two hours by a saline cathartic.

Flukes

Schistosoma Haematobium, S. Mansoni, S. Japonicum. Infestation with these parasites, commonly known as the blood flukes, is known as *schistosomiasis.* This disease is widespread throughout the Orient, Africa, Western Asia and Northern Brazil. The various species of Schistosoma, however, are more discrete in their distribution. Inasmuch as many of the symptoms produced by the aforementioned parasites are similar and the therapy against all three forms is identical, they will be discussed together.

The adult forms of *Schistosoma haematobium* live in the vesical and pelvic venous plexuses; *S. mansoni,* in the mesenteric venules draining the large bowel and lower portion of the ileum; *S. japonicum,* in the mesenteric vessels of the upper portion of the intestinal tract. The eggs are laid in these veins and work their way into the bladder or intestinal wall and reach the exterior through the urine or feces. The eggs hatch in water and the larvae, utilizing snails and mollusks as intermediary hosts, develop to a stage known as *cercariae,* which are infective for man, in whom they gain entrance by penetrating the skin to reach the venules. The three species accumulate in the portal blood where they develop to the adolescent stage and then migrate to their characteristic locations.

The symptoms of all types of schistosomiasis can be grouped into three stages, those occurring during the (1) incubation period, (2) the period of egg deposition and extrusion, and (3) the period of tissue proliferation. The incubation period lasts one to three months and includes the interval between the invasion of the skin by the cercariae and the beginning of egg deposition by the adult female. Invasion of the skin is characterized by a local cutaneous reaction, and minute petechiae are formed where the larvae penetrate the blood vessels. The end of the incubation period is accompanied by a marked systemic reaction, especially in the case of infestation with *S. haematobium.* The symptoms are anorexia, headache, malaise, pain in the back and extremities, urticaria, fever, enlarged and tender abdomen and enlargement of the liver and spleen.

The symptoms of the second stage, that of egg deposition, depend upon the location of the parasite. The extrusion of the egg results in severe local inflammatory reactions with abscess and pseudotubercle formation. When the infesting organism is *S. haematobium,* the bladder, ureter and urethra are seriously involved. The intestinal wall is injured by the other two parasites. In the third stage, that of tissue proliferation and repair, a marked hyperplasia of the affected organs occurs and symptoms depend upon the resulting functional impairment.

Treatment. In the therapy of schistosomiasis, one must resort to anthelmintics which can be absorbed into the systemic circulation and there exert a selective toxic action on the parasite. The most effective preparations yet discovered are antimony compounds. Those employed are *antimony and potassium tartrate, antimony and sodium tartrate* and *antimony pyrocatechin sodium disulfonate.* The last-named drug is also variously known as "fouadin", "pyrostib" and "neoantimosan" and can be injected intramuscularly. The tartrates are extremely irritating to tissues and must be given by intravenous injection.

The tartrate salts must be given intravenously in freshly prepared solutions. The concentration injected varies, some physicians employing one per cent solutions, others using concentrations as high as six per cent. The drug is usually given in courses of four weeks duration, during which a total of 1.3 to 2.0 grams of the tartrate salt is injected. Injections are made three times weekly, the first two being made in doses of 60 and 90 mgm respectively, and the remainder, 120 to 130 mgm. If fouadin is employed, the usual course lasts 15 days. The drug is injected intramuscularly in seven per cent solution. On the first day 1.5 cc, on the second 3.5 cc and on the third 5.0 cc are administered. This last amount is then given on alternate days until a total of 40 cc has been injected. Fouadin is said to be as effective as the tartrate salts and to cause fewer side-actions and toxic symptoms (*see* antimony).

The success of therapy depends upon early diagnosis and prompt treatment. If the disease has reached the chronic stage characterized by tissue change, little can be accomplished.

Many other drugs have been used in schistosomiasis. Emetine is occasionally employed when patients are intolerant to antimony, but it is less effective. Of the many available organic antimony preparations, those described have proved to be the most serviceable.

Paragonimus Westermanni. This fluke is prevalent in the Far East but cases have been reported in Mexico. Man becomes infested by eating crabs containing cercariae. The encysted cercariae are liberated in the duodenum. They then migrate through the intestinal wall, abdominal cavity, diaphragm, and pleural cavity to invade the lungs where they become encysted near bronchioles and cause the condition known as pulmonary distomiasis.

Symptoms. The organisms in the lung give rise to a leukocytic infiltration which is followed by the development of a thick fibrous tissue layer which encapsulates the parasite. Symptoms are cough, hemoptysis and pain. Often the cercariae go astray in their migration and may encyst in almost any other organ. Symptoms will then vary with the organ involved.

Treatment. Emetine hydrochloride is the only drug with any effect on this particular species of fluke, but results are often disappointing. It is given in courses in exactly the same manner as outlined in the treatment of amebiasis.

Clonorchis Sinensis. Infestation with this fluke is prevalent in the Far East. The parasites gain access to the human host following the ingestion of infected fish, migrate through the common bile duct to the distal biliary passages where they mature to the adult form.

Symptoms. These vary in severity and depend upon the degree of liver impairment. Heavy infestation may lead to severe portal cirrhosis. Systemic reactions include tachycardia, skeletal muscle tremors and cramps, and mental depression.

Treatment. Early cases respond quite well to intravenous *sodium antimony tartrate.* The technic outlined for the treatment of schistosomiasis is followed. *Gentian violet* is also an effective drug. It is given in 0.06 gram enteric capsules three times daily before meals for a month. In heavy infestations, therapy can do no more than reduce the number of invading organisms and hence the severity of symptoms.

Fasciolopsis Buski. This fluke is prevalent in the Orient. Man becomes infested by eating water plants containing encysted cercariae, and the adult forms attach themselves to the walls of the duodenum and jejunum.

Symptoms. Symptoms include those of inflammation and ulceration of the intestinal wall. In addition, the worms cause a generalized toxemia which may be fatal.

Treatment. Carbon tetrachloride and *tetrachlorethylene* are very effective against this infestation. The drugs are given in exactly the same manner as for hookworm. *Betanaphthol* is also effective but not to be preferred.

Heterophyes Heterophyes. Infestation with this parasite is common in the Nile delta and the Orient. Man becomes infected by eating fish containing cercariae, and adult worms attach themselves to the wall of the small intestine. Symptoms include severe colic and mucous diarrhea. *Carbon tetrachloride* and *tetrachlorethylene* administered in the usual manner are very effective in the treatment of this infestation.

Metagonimus Yokogawai. This fluke infests the population of the Sino-Japanese area, the northern provinces of Siberia, the Balkan States and Spain. Human infestation results from the ingestion of undercooked fish containing cercariae, and the adult worm inhabits the small intestine. Diarrhea is the most common symptom. The infestation responds very well to *tetrachlorethylene* and *carbon tetrachloride* given in the usual manner.

Gastrodiscoides Hominis. This species of fluke is prevalent in India and Assam. The adult parasites are attached to the wall of the cecum and ascending colon and cause diarrhea. Effective anthelmintics are *carbon tetrachloride* and *tetrachlorethylene* given in the usual manner.

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CHAPTER 50

DRUGS USED IN THE CHEMOTHERAPY OF MALARIA

QUININE, PLASMOCHIN AND ATABRINE

QUININE AND THE CINCHONA ALKALOIDS

Historical. Quinine is the chief alkaloid of cinchona, the bark of the cinchona tree which is indigenous to certain regions of South America.

The bark is also called Peruvian, Jesuit's or Cardinal's bark. It is not clear whether the natives were acquainted with the medicinal properties of cinchona and there is some evidence that they viewed it as a toxic substance. The first mention of the use of cinchona in fever is the case of a Spanish official in Ecuador who was cured of malaria in 1630. Eight years later, this person is said to have suggested that the bark be employed to treat the fever of the Countess Anna del Chinchon, the wife of the Viceroy to Peru. Juan del Vego, the physician attending the Countess, was so impressed by the miraculous cure that he introduced cinchona into Spain in 1639 for the treatment of ague. By 1640, the use of the drug had spread over Europe.

The term cinchona was chosen by Linné for the species of plants yielding the drug. This term is thought to be derived from the name of the Countess whose cure led to its wide use, and for some time the medicine was called "polvo de la condesa." Others believe it comes from a word of Inca origin, "kinia," which means bark. The Jesuit fathers were the chief importers and distributors of cinchona in Europe and the name Jesuit bark soon became attached to the drug. The conservative medical groups viewed the new antipyretic with disdain because its use did not conform to the teachings of Galen. Others looked upon it with suspicion because the Jesuits sold it. For these reasons, many charlatans were successful in employing the bark in secret remedies. The first official recognition of cinchona came in 1677 when it was included in an edition of the London Pharmacopoeia under the title Cortex Peruanus.

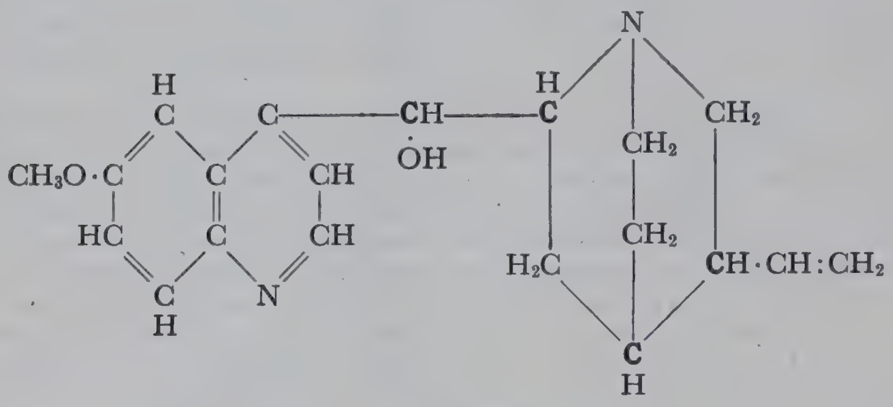
For almost two centuries the bark was employed in medicine as a powder, extract, or infusion. In 1820, Pelletier and Caventou isolated quinine and cinchonine from cinchona, and the use of the alkaloids as such gained favor rapidly.

Source. Quinine and its related alkaloids are obtained from several species of two rubiaceous genera, *Cinchona* and *Remijia* (*Cuprea*), which are native on the high eastern slopes of the Andes. These trees have special growth requirements, and their cultivation in other parts of the world has met with many difficulties. The indiscriminate removal of the bark caused the cinchona trees to die, and the resulting high price of quinine during the middle of the 19th century was an impetus for planting the trees in other parts of the world. The Dutch East Indies Government spent considerable time and money studying the chemical and botanical aspects of the problem, and as a result the chief source (more than 90 per cent) of quinine today is from the trees cultivated in Java. The species known as *Cinchona ledgeriana* is grown there and yields the highest percentage of quinine. Its total content of alkaloid is six per cent, and 70 per cent of this is quinine. India and Ceylon also have plantations for cinchona, and the *succiruba* species which is cultivated there yields six per cent total alkaloids but only 30 per cent of this is quinine. It is said that more than 600 tons of quinine are produced annually, but this is only a small amount of what is really needed to supply adequate therapy to all those with malaria.

Chemistry. The cinchona alkaloids are obtained from the bark of the roots, trunk and branches. There are reasons for believing that these drugs are metabolic waste products of the tree. The chemist has failed to synthesize quinine, which must therefore be obtained entirely from natural sources. Many new series of drugs and chemicals nevertheless have been produced in the laboratory by alteration of the quinine molecule.

Cinchona contains a mixture of more than twenty alkaloids. The most important of these are two pairs of isomers, *quinine* and *quinidine,* and *cinchonidine* and *cinchonine.* Quinine and cinchonidine are levorotatory and the remaining two compounds are dextrorotatory. The chemical structure of the cinchona alkaloids has received considerable attention. Inasmuch as hundreds of compounds have been derived from quinine or its congeners, each differing in its chemical and pharmacological properties, this field has offered a promising opportunity for the study of the relationship between chemical structure and pharmacological effect. It is interesting, therefore, to examine the component parts of the quinine molecule.

The structure of quinine is shown in the following formula which presents the four asymmetric carbon atoms in bold-faced type:



Quinine

An inspection of this compound shows that it is built on a definite pattern. A quinoline ring (Q) is attached through a secondary alcohol linkage (A) to a quinuclidine ring (Qn), schematically presented as follows: Q + A + Qn. In addition, there are two side-chains, alterations of which form the basis for the many natural alkaloids and synthetic chemicals derived from quinine. One of these side-chains (S_1) is attached to the quinoline, and in quinine this is a methoxy group. The other is attached to the quinuclidine ring, and is a vinyl group ($-CH=CH_2$) in quinine. Thus quinine is schematically: methoxy + Q + A + Qn + vinyl. Quinidine is the same as quinine except that it is dextrorotatory due to a difference in the configuration of the secondary alcohol grouping (A). Cinchonidine and cinchonine differ from quinine in that they have no methoxy group in S_1 position, and can be written as: Q + A + Qn + vinyl.

The many changes possible in this pattern are obvious, but may be illustrated at this juncture by the examples of two chemicals, *cupreine* and *hydroquinine.* The latter is synthetic but cupreine is a natural alkaloid of cinchona. In cupreine, the S_1 is occupied by OH; in hydroquinine, which is obtained from quinine by reduction with hydrogen, S_2 is no longer a vinyl group but $-CH_2CH_3$. The schematic formulas for these substances may be presented as follows:

Cupreine: $OH + Q + A + Qn + CH{:}CH_2$
Hydroquinine: $CH_3O + Q + A + Qn + CH_2CH_3$

Quinine is thus methyl cupreine and hydroquinine is methyl hydrocupreine. In a sense, the alkaloid cupreine is really the parent substance. Each alteration in the pattern of quinine causes changes in the actions of the compound.

Relation of Chemical Structure to Pharmacological Action. All the natural cinchona alkaloids and many of the synthetic derivatives of quinine manifest, in a qualitative way, the same pharmacological properties. The effects of chemical alterations on the antimalarial action of these drugs have received particular attention. *Cinchonine* is less effective against plasmodia than is *cinchonidine* which approaches quinine in its antimalarial efficacy and general pharmacological properties. That antimalarial action is not confined to levorotatory compounds, however, is seen from the results obtained with *quinidine.* Sanders (1936), for example, reported that he used quinidine in the same manner and dose as quinine in more than thirteen hundred malarial patients in private practice and found it somewhat superior to quinine. *Cupreine,* which lacks the methoxy group in the quinoline side-chain, is less toxic and less effective against plasmodia than is quinine. The methoxy group of quinine therefore appears to be helpful but not essential for the action of quinine in malaria. Demethylation may be one of the means by which the body detoxifies quinine.

The *vinyl* group on the quinuclidine part of the molecule is not needed for antimalarial action. When it is changed by hydrogenation to an ethyl group to form *hydroquinine,* the potency is actually increased. The *secondary alcohol* linkage between the quinoline and quinuclidine portions of quinine is absolutely essential for plasmodicidal power, and the reduction of this group increases toxicity and abolishes antiplasmodial potency. Steroisomerism about this alcohol link does not alter materially the antimalarial efficacy. The further details of this interesting field of interrelations between chemical changes and pharmacological properties must be sought in special works (*see* von Oettingen, 1933). The importance of these studies lies in the possibility of obtaining more effective and less toxic compounds.

The typical action of cinchona is attributable to its quinine content. Whereas this alkaloid constitutes at least five per cent by weight of the dried commercial bark, the other natural alkaloids comprise less than one-half per cent each. In the following pages, the pharmacology of quinine will be presented, and the important variations in action of related alkaloids will be pointed out as occasion arises.

Pharmacological Actions

Local. Quinine is usually stated to be a "general protoplasmic poison," and with some reservations this appraisal is correct.

Like many other poisons of this sort, it stimulates in low concentrations and depresses in high concentrations. Quinine inhibits Brownian activity of colloids, depresses many fermentative processes, interferes with phagocytosis, depresses ciliary activity of epithelium, inhibits growth of fibroblasts in tissue culture, and restricts a number of the chemical reactions in the body. It is toxic to bacteria and many unicellular organisms including trypanosomes, infusoria, yeast, plasmodia and spermatozoa. The many actions of quinine, however, present striking peculiarities. Moulds grow freely in quinine solutions. High concentrations of the drug are required to kill sperm cells or bacteria. Salt water amebae are far more resistant to quinine than are fresh water amebae. Similarly, mouth spirochetes are very susceptible to the alkaloid but the pathogenic spirochetes of relapsing fever are unaffected. It is thus clear that quinine is quite specific in the type of protoplasm which it affects.

The mechanism of the general protoplasmic toxicity of quinine is unknown. Some attribute it to the action of the alkaloid on intracellular enzymes. Others focus attention on the tendency of the drug to form films on surfaces of colloidal solutions and in this way to alter cell permeability and interfere with cell activity. It has been suggested that the formation of a quinine film on red corpuscles may be the mechanism of the antimalarial action of this alkaloid.

Action on Ferments. The action of quinine on a large number of enzymatic processes in plants and animals has been investigated. Yeast fermentation is inhibited, the invertase reaction is diminished, autolytic tissue ferments are depressed and the activity of rennet and lipase is decreased. The concentration of drug, the pH of the solution, and the presence of serum greatly modify this action of quinine. Most of this work on enzymes has been done with high concentrations of drug and there is little indication that concentrations obtainable from therapeutic doses of quinine in man seriously affect the ferments of the body.

Action on Bacteria. It has been known since Pringle's publication in 1765 that cinchona powder prevents meat from putrefying. A high concentration of quinine is needed to kill bacteria and dilute solutions may even stimulate the growth of certain organisms. At one time, quinine solutions were used for purposes of antiseptic irrigation. Certain derivatives of quinine exhjbit highly selective toxicity for specific bacteria. Thus, ethylhydrocupreine is effective under certain conditions against the pneumococcus and octylhydrocupreine against the diphtheria bacillus.

Local Anesthetic Action. The cellular toxicity of quinine is also manifested in its action on sensory nerves which are briefly stimulated and then paralyzed. The efficacy of quinine and its derivatives as local anesthetics is dependent on and directly proportional to their toxicity for protoplasm (Dixon and De, 1927). Concentrations only slightly higher than necessary for anesthesia are likely to cause edema, pain and reactive fibrosis. The anesthesia may last for many hours or days, and in this respect differs sharply from that of cocaine and the other local anesthetics.

Irritant Action. Quinine is a marked local irritant. When taken orally, it may cause gastric pain, nausea and vomiting. When given in solution rectally, the ensuing irritation may result in its rapid expulsion. The initial action on sensory nerves is also one of irritation. Subcutaneous or intramuscular injections are painful and sterile abscesses may result from local tissue damage. Intravenous injection may be complicated by thrombosis of the vein, due to injury of the intima.

This vascular damage is the basis for the use of quinine solutions in the *sclerosing of varicose veins.* The irritant properties of quinine also appear where the drug is concentrated at the channel of excretion from the body, and thus renal injury may occur.

Antipyretic Action. The discovery that cinchona lowered the fever of malarial patients quickly led to its use in all forms of febrile illnesses. The striking effect of quinine on the fever of malaria is due to the specific action of the alkaloid on the cause of the disease. The rather indifferent results on other fevers is testimony to the fact that quinine is not a potent antipyretic. For many years it was believed that quinine differed from other fever-reducing drugs in that it depressed metabolism, prevented protein breakdown and decreased heat production. It is now known that quinine has no such action on metabolism (Hardikar, 1925) and that it acts in reducing fever in a manner similar to other antipyretics (page 226).

Like other agents in this class, the effect of quinine on normal body temperature is negligible. Two grams of the drug cause practically no fall in the temperature of a normal adult. Toxic doses of quinine (four grams) cause a reduction in temperature, both by increased heat loss and depressed heat production. Compared with drugs such as the salicylates and the pyrazolon and paraminophenol derivatives, quinine is a rather poor antipyretic. Its action is not as rapid, potent or certain, but it may persist for a longer time. The occurrence of early toxic symptoms from full doses of quinine also limits its usefulness.

Analgesic Action. Quinine resembles the salicylates and related drugs in possessing analgesic potency. This action results in an obtundation of pain sense, especially that arising in muscles and joints. The site of action is central, but beyond this fact little else is known regarding its localization. Quinine can be used for analgesia in a manner similar to that of other members of the analgesic and antipyretic group of drugs.

Metabolic Effects. As was indicated above, quinine for many years was believed to have a depressant effect on metabolism. In this way, heat production was thought to be lessened and fever reduced. It is now known that the experiments on which these conclusions were based were faulty (Hardikar, 1924), and therapeutic doses of quinine in man cause no derangement of protein metabolism. Quinine can lower the *blood sugar* of normal as well as of diabetic subjects if moderate doses are given intravenously. The mechanism is unknown. The supposition that quinine depresses metabolism led to its use in *hyperthyroidism*. Clinical reports of its efficacy are not in agreement but there is some indication that patients with hyperthyroidism are tolerant of doses of quinine which are toxic for normal people.

Central Nervous System. Therapeutic doses of quinine have few effects on the nervous system other than to cause analgesia and antipyresis. Small amounts of the drug tend to increase the acuity of hearing of some individuals. Toxic amounts of the alkaloid first briefly stimulate and then markedly depress the central nervous system, as described under quinine poisoning. Certain quinine derivatives, particularly cinchonidine, are convulsant in large amounts and quinine itself manifests this action in certain species. The convulsions sometimes seen in man after toxic doses of quinine are probably asphyxial in character. Therapeutic doses have practically no effect on respiration, but poisoning is characterized by central stimulation of breathing followed by respiratory depression which is the cause of death.

Cardiovascular System. The effect of quinine on heart muscle is qualitatively similar to that of its isomer, quinidine. This action is described in full under quinidine and auricular fibrillation. Therapeutic doses of quinine have little if any effect on the normal heart or blood pressure. Large doses (above five grams) directly depress the heart and this accounts in part for the low blood pressure which occurs in quinine poisoning. The action of quinine on blood vessels is generally one of vasodilatation by a direct peripheral action on the smooth muscle of the vessel wall. It is not antagonized by epinephrine or sympathetic nerve stimulation but is counteracted by barium and posterior pituitary extract. In man, doses slightly larger than those used clinically cause flushing of the skin. The vasodilatation is noticeable especially in the extremities. The splanchnic capillary bed is affected only slightly or may even show a compensatory constriction. Vasodilatation is marked in quinine poisoning and largely accounts for the low blood pressure. When given intravenously, quinine causes a definite and sometimes alarming fall in blood pressure. This is noted particularly when the injection is made rapidly. It has been explained as due either to a direct myocardial depression or a flocculation phenomenon.

Uterus. The action of quinine on the *uterus* was first observed by Monteverdi in 1872. The uterus, either *in situ* or excised, is stimulated by the alkaloid in moderate doses and depressed by large amounts. The non-gravid uterus is slightly affected but as pregnancy proceeds the oxytocic action of quinine becomes progressively more noticeable. Clinically, quinine is rather ineffective until labor has actually begun. Although quinine has been used with other adjuvants to initiate labor, it cannot be considered a potent or indispensable uterine stimulant and its action is unreliable.

The oxytocic action of quinine and related alkaloids is poorly understood. The drug does not produce uterine spasm as does ergot or pituitrin, and appears only to intensify the periodic but weak labor pains. Toxic amounts of quinine may cause abortion, but it is questionable whether this is always due to a direct uterine action of the drug. Quinine also passes into the circulation of the fetus where it can produce poisoning.

Other Smooth Muscle. The *spleen* may contract as a result of the action of quinine on the smooth muscle in its capsule. This is thought to be the cause of the lymphocytosis sometimes observed after therapeutic doses of the drug. The *intestinal* musculature may also be stimulated as has been shown by *in vitro* experiments. The tone is decreased but the amplitude is increased by synchronous contraction of both muscle coats of the intestine. There is no evidence, however, of any such effect in the clinical use of quinine. On rare occasions, quinine constricts *bronchial* muscles and causes asthma. This is a matter of individual idiosyncrasy.

Skeletal Muscle. It has long been known that cinchona alkaloids in high concentration produce marked skeletal muscle rigor. Lower concentrations cause an increase in the tension response of a muscle to a single maximal stimulus delivered directly or through the nerve. This mechanical potentiation is due to a direct effect of quinine on the muscle cell and is accompanied by an increase in amplitude and duration of the muscle action potential (Harvey, 1939). After administration of quinine, skeletal muscle is unable to maintain a tetanus due to an increase in the refractory period of the muscle fiber. Quinine also possesses a direct curare-like action on skeletal muscle. When the alkaloid is administered to a partially curarized muscle, the curarization is completed. The refractory period is increased and the excitability of the motor end-plate is decreased, and thereby both the response to a tetanizing stimulus and to acetylcholine are diminished or prevented. Quinine prevents or counteracts the normal potentiation of muscular twitches caused by physostigmine and prostigmine which are due to repetitive responses to a single nerve volley. Quinine also prevents the repetitive response to a single stimulus which occurs after veratrine. In addition, the drug abolishes the high sensitivity of denervated muscle to acetylcholine. The locus of action of quinine appears to be directly on skeletal muscle, perhaps particularly on the end-plate. The activity of cholinesterase is not enhanced by quinine; indeed, it is slightly inhibited. That the effects of quinine in counteracting the responses to acetylcholine and anticholinesterase drugs may not be confined to skeletal muscle is suggested by the experiments of Stavraky (1933) on the submaxillary gland.

The effects of quinine and related alkaloids on skeletal muscle remained purely a matter of academic interest until the surprising fact was demonstrated that myotonia congenita could be symptomatically relieved by quinine (Wolf, 1936). This disease is the "pharmacological opposite" of myasthenia gravis (page 342), and investigations soon revealed that drugs which are effective in one syndrome aggravate the other. Thus, quinine increases the muscular weakness of patients with myasthenia gravis and has diagnostic usefulness in early questionable cases of the disease when prostigmine produces only equivocal improvement (Harvey and Whitehill, 1937). Quinine may so aggravate the symptoms of myasthenia that alarming respiratory distress and dysphagia may ensue. Also, in patients with myasthenia gravis who are well controlled by prostigmine therapy, quinine causes the return of symptoms. Conversely, prostigmine aggravates the symptoms of myotonia congenita and can completely counteract the beneficial effects of quinine in this disorder. For details of this rapidly advancing field, the interested reader is referred to the publications of Kennedy and Wolf (1938), Harvey (1939), Oester and Maaske (1939), and Briscoe (1939).

Blood. *Red Blood Cells.* Red blood cells will hemolyze when placed in a solution of 0.25 per cent quinine. Inasmuch as this concentration is never reached clinically, even when the drug is injected intravenously, the occasional hemolytic reactions to quinine noted in man cannot be explained by this direct action. Experimentally, small amounts of quinine have been noted to increase the amboceptor hemolysis of red blood corpuscles *in vivo,* and also to potentiate the lytic action of cobra venom. The latter action is antagonized by cholesterol, and it has been suggested that the hemolysis noted after quinine medication in blackwater fever may be related to the low cholesterol values reported to occur in some of these patients.

Action on Leukocytes. Quinine inhibits phagocytosis by leukocytes in a dilution of 1:3000 and is toxic to these cells in dilutions of 1:1000. These concentrations are not reached clinically, but if large doses are given to animals leukopenia may occur. With the exception of a rare questionable case, no instances of malignant neutropenia have been reported from quinine medication in man. Therapeutic doses of quinine in man have been found to cause a primary increase in white blood cells due to an increase in the number of lymphocytes, perhaps as a result of contraction of the spleen. This is then followed in an hour or two by leukopenia due to a reduction in polymorphonuclear elements. There then appears a final stage of polymorphonuclear leukocytosis. Whether quinine effects these changes through a direct action on white cells or through their redistribution in the body is not known. There is some evidence that high dilutions of the drug stimulate leukocytic activity, and the opsonic index is said to be slightly elevated after clinical doses. None of these actions forms the basis for therapeutic applications of quinine.

Gastro-Intestinal Tract. The soluble salts of quinine are extremely bitter and very small amounts of cinchona preparations are used as *stomachics.* Larger doses may inhibit gastric secretion. The irritant properties of these alkaloids cause considerable *gastric distress.* Nausea, vomiting and diarrhea are prominent when large doses are taken orally. Toxic amounts also produce vomiting by a central action on the medulla. The *musculature* of the intestinal tract is not stimulated by concentrations of the drug reached clinically, and the apparent success obtained in cases of constipation from the use of quinine suppositories or enemata must be attributed to the local irritant action of the drug on the mucosa of the bowel.

Absorption, Fate and Excretion. *Absorption.* Quinine given orally is absorbed mainly from the small intestine. Absorption of most quinine salts is sufficiently rapid to make the oral route the most satisfactory one for quinine administration. The rectal absorption of quinine is poor and inconstant due mainly to the local irritant effects and the tendency to expel solutions given in this manner. When quinine is injected subcutaneously, it is precipitated from its salt as the free alkaloid and may remain unabsorbed at the injection site for many days. Tissue damage from parenteral administration may result in abscess formation or sloughing, especially if the solutions employed are too concentrated. Quinine injected intramuscularly does not appear in the urine as early as that given by mouth.

Fate. Sixty to 70 per cent of the administered quinine is rapidly destroyed in the body, especially by the liver but also by the kidneys and muscles. The concentration of quinine in the blood and its distribution between serum and cells have received considerable attention. Attempts have been made to explain the action of quinine in malaria on the basis of the amount of alkaloid in the circulation or its concentration on red blood cell surfaces. After intravenous administration, quinine leaves the blood so rapidly that only a trace remains after a few minutes. A considerable part of the alkaloid is taken up by the endothelium of the capillaries, as can be demonstrated by perfusing the vessels and regaining the drug. Upon oral administration (0.65 gram every four hours), the blood concentration of quinine reaches only 10 mgm per liter. This concentration is far below that necessary to cause a direct plasmodicidal effect in malaria. When present in concentrations above 10 mgm per liter of blood, quinine produces very toxic effects. Investigations of the distribution of the drug between cells and serum have yielded widely divergent results. The best evidence shows that the cell concentration is somewhat higher than that of the serum, but the cell to serum ratio has nevertheless been variously reported to be from 1:3 to 1:0.2.

Excretion. Regardless of the route of administration, the main channel of excretion of quinine is the urine, but small amounts of the drug also appear in the feces, the gastric juice, bile and saliva. About one-third of the administered quinine appears in the urine. It can be detected within 15 minutes after the drug is ingested and reaches its maximal concentration within four hours, regardless of the dose taken. Urinary excretion continues at this high level for another four hours and then gradually tapers off. Excretion of a single dose is practically complete in 24 hours but traces of quinine can be detected for several days. Excretion is delayed in cases of severe nephritis, and when the liver is damaged more quinine escapes by way of the kidney. Because both urinary excretion and liver destruction of quinine are rapid, the interval between oral doses of the alkaloid should be about four hours.

Toxicology. The toxic reactions to quinine and other cinchona alkaloids are similar. It is sometimes difficult, however, to distinguish between true quinine toxicity and untoward reactions resulting from the disease for which the drug is given. Again, quinine poisoning is occasionally difficult to differentiate from reactions due to hypersensitivity.

Symptoms. Poisoning by quinine is usually due to overdosage in the clinical use of the drug or to idiosyncrasy. The fatal oral dose of quinine for adults is approximately eight grams. Survival has been reported after the ingestion of much larger amounts, but absorption may have been incomplete.

When quinine is repeatedly given in full doses, a typical train of symptoms occurs to which the term *cinchonism* has been applied. The syndrome of cinchonism is caused not only by the cinchona alkaloids but also by the salicylates and cinchophen. In its mildest form it consists of ringing in the ears, headache, nausea and slightly disturbed vision, but when medication is continued or after large single doses the symptoms extend to the gastro-intestinal tract, nervous and cardiovascular systems, and the skin.

Hearing and vision are particularly involved. The functional impairment of the eighth nerve results in tinnitus, decreased auditory acuity and vertigo. The visual signs are those of blurred vision and disturbed color perception, photophobia, diplopia, night blindness, constricted visual fields, scotomata and dilated pupils. The terms "quinine amblyopia" and "quinine amaurosis" have arisen as a result of the frequency of these findings in the more severe grades of intoxication. Considerable investigation into the mechanism of the optic and auditory nerve involvement has failed to establish whether quinine exerts its deleterious action secondarily through vascular changes in the retina and organ of Corti or through a primary injury to the ganglion cells and nerve fibers. Attention has been directed repeatedly to the marked spastic constriction seen in the retinal vessels. The retina is ischemic, the discs are pale and edema may follow. In severe cases, optic atrophy results. Degenerative changes in the spiral ganglion cells similar to those noted in the ganglion cells of the retina lend support to the belief that the cellular injury from quinine is direct. Other work tends to support the vascular basis for the lesions. The use of quinine by pregnant women is thought to be a cause of congenital deafness or blindness (Richardson, 1936; West, 1938).

Gastro-intestinal symptoms are also prominent in cinchonism. Nausea, vomiting, abdominal pain and diarrhea occur, largely due to the local irritant action of quinine but the emesis also has a central basis. The *skin* is often hot and flushed and sweating is prominent. Rashes frequently appear and these may be papular, scarlatiniform or urticarial in character. Angioneurotic swelling and inflammatory edema of the face are occasionally seen. The *central nervous system symptoms* are noted in severer grades of poisoning. There are headache, fever, vomiting, apprehension, excitement, confusion and syncope. *Respiration* which at first is stimulated becomes shallow and depressed. Delirium and coma occur terminally. The skin becomes cold and cyanotic as poisoning progresses, the body temperature and blood pressure fall, weakness is extreme, the pulse is feeble, and death occurs usually in coma from cessation of respiration. *Death* may result in a few hours or be delayed a day or two. If recovery occurs, it is usually complete except that in some cases there are various grades of residual optic and auditory damage.

At times, *renal damage* may be evident and anuria and uremia ensue. *Red blood cells* may rarely hemolyze and the urine then contains free hemoglobin. This usually occurs only when quinine is given in malaria due to the plasmodium falciparum, but hemoglobinuria has occasionally appeared in non-malarial pregnant women. Pregnant women may abort as a result of quinine overdosage but this is not necessarily due to an oxytocic action of the drug. *Asthma* may ensue in sensitive individuals.

Treatment. Inasmuch as quinine is rapidly destroyed by the liver and excreted by the kidneys, the longer the patient survives the better the prognosis becomes. Absorption may be slow if fairly insoluble salts have been ingested. The stomach, therefore, should be copiously lavaged with water through the gastric tube, and alkaloidal precipitants employed if they are available. Magnesium sulfate should be placed in the stomach to hasten the passage of the unabsorbed poison from the bowel. The blood pressure is supported and symptomatic measures employed to maintain renal function and overcome central depression. Caffeine, ephedrine, carbon dioxide and oxygen, and even artificial respiration may be needed to combat respiratory failure. Body temperature should be maintained. Hemoglobinuria may necessitate blood transfusion and the use of alkalis (page 246). Angioneurotic or asthmatic phenomena may require the use of epinephrine. After recovery, visual impairment occasionally yields to vasodilators such as nitrites and mecholyl in a manner similar to the toxic amblyopia from tobacco. Bromides are said to relieve the tinnitus in milder degrees of poisoning.

Idiosyncrasy. When toxic manifestations appear from the use of small doses of cinchona alkaloids, the individual is usually hypersensitive to the drug. Cinchonism may appear after a single dose of quinine but it is usually mild. Skin rashes, fever, gastric distress, dyspnea, ringing in the ears and visual impairment are the commonest expressions of hypersensitivity. Hemoglobinuria and asthma from quinine are rare forms of idiosyncrasy. All these have been discussed under quinine poisoning.

The skin sensitivity to quinine can be revealed by means of the scratch test using a one to 10 per cent solution of a quinine salt in physiological saline solution. Within five to 15 minutes, redness, edema and itching will appear if the patient is hypersensitive. The absence of a positive reaction cannot be relied upon to exclude the possibility of idiosyncrasy. The positive skin response to quinine often extends to other levorotatory cinchona alkaloids but only rarely to the dextrorotatory compounds. Thus, Dawson and Garbade (1930) showed that individuals responding with a positive skin test to quinine also responded to the levorotatory hydroquinine, cupreine, hydrocupreine, ethylhydrocupreine, and cinchonidine; but the cutaneous reaction to such dextrorotatory compounds as quinidine, cinchonine, hydrocinchonine, hydrocupreidine, and ethylhydrocupreidine was negative. This fact allows the use of quinidine in malarial patients sensitive to quinine.

Desensitization. Patients sensitive to quinine sometimes can be desensitized. This is accomplished by giving a small oral dose of quinine (five mgm) with 0.5 gram sodium bicarbonate and then giving 0.1 gram quinine with 0.5 gram of the alkali one-half hour later. These two doses are repeated daily, but the second dose of quinine is elevated by 0.1 gram each day until a full therapeutic dose can be taken without untoward effects. The positive skin test becomes less pronounced as desensitization proceeds.

Contraindications. Quinine must be used with caution in patients who manifest idiosyncrasy to it, especially when this takes the form of cutaneous, angioneurotic, visual or auditory symptoms. Also, pregnant women near term should not be given quinine unless absolutely necessary. Quinine should be stopped immediately if evidence of hemolysis appears. The presence of optic neuritis also contraindicates the use of cinchona alkaloids. If the auricles are fibrillating, the use of quinine requires the same precautions as outlined for quinidine.

Preparations, Doses, and Routes of Administration. There are numerous preparations of cinchona alkaloids available for the practitioner, particularly in tropical communities where malaria is endemic and where cheap cinchona medication is essential. In the United States, the pure alkaloids are most frequently employed. *Quinine,* U.S.P., B.P., is a white, microcrystalline, odorless powder, and has a bitter taste which is intense and persistent. It is efflorescent in dry air and is soluble in water 1:1560 and in alcohol 1:0.8. Quinine forms a large number of salts, many of which are official in the U.S.P., B.P., and N.F. Most of the quinine salts are white crystalline powders which are intensely bitter. In acid solution, they have a blue fluorescence. Only the insoluble salts are relatively tasteless. This is true, for example, of *quinine ethylcarbonate* (euquinine) and *diquinine carbonate* (aristochine). These esters are saponified in the small intestine and are slowly absorbed.

The official salts of quinine, their status and water solubilities are as follows:

Quinine Salt	*Status*	*Water Solubility*
Quinine Bisulfate	U.S.P., B.P.	1:9
Quinine Dihydrochloride	U.S.P., B.P.	1:0.6
Quinine Ethylcarbonate	U.S.P., B.P.	sl. sol.
Quinine Hydrobromide	N.F.	1:40
Quinine Hydrochloride	N.F., B.P.	1:16
Quinine Phosphate	N.F.	1:600
Quinine Salicylate	N.F.	sl. sol.
Quinine Sulfate	U.S.P., B.P.	1:810
Quinine Tannate	B.P.	sl. sol.
Quinine and Urea Hydrochloride	U.S.P.	1:0.9

Of the commonly employed salts, the dihydrochloride and bisulfate are most soluble and are to be preferred. A number of quinine preparations are rarely used, including the phosphate, salicylate and tannate. *Quinine and urea hydrochloride* is the salt employed as a local anesthetic and sclerosing agent, but its solutions are strongly acid. *Quinine Hydrochloride and Urethane* (N.F.) is to be preferred as a sclerosing agent because its aqueous solution is neutral.

In addition to the preparations listed, a number of mixtures exist which contain quinine. These include *Elixir of Iron, Quinine and Strychnine* (Elixir I.Q. & S.), N.F., *Elixir of Iron, Quinine and Strychnine Phosphates* (Elixir I.Q. & S. Phosphates), N.F., *Pills of Iron, Quinine, Strychnine and Arsenic,* N.F., *Iron and Quinine Citrate,* B.P., and *Syrup of Ferrous Phosphate with Quinine and Strychnine,* B.P. These preparations are unnecessarily complex, represent irrational therapeutic survivals, and are not recommended, despite the wide use some of them enjoy, especially *Elixir of I.Q. & S.*

Cinchona and its galenical preparations are rarely used in therapeutics in the United States. Official preparations are as follows: *Cinchona* (Peruvian Bark), U.S.P., B.P., *Extract of Cinchona,* B.P., *Fluidextract of Cinchona,* U.S.P., B.P., *Tincture of Cinchona,* B.P., *Compound Tincture of Cinchona,* U.S.P., B.P. and *Elixir of Cinchona Alkaloids,* N.F. The N.F. also contains *Cinchonine Sulfate* and *Cinchonidine Sulfate.* The chemistry of this pair of alkaloids has already been described.

The usual oral dose of quinine or its salts is 0.3 to 0.6 gram, and the total daily dose is rarely more than 2.0 grams. *Tolerance* does not develop to quinine, and this dose therefore does not have to be increased even after prolonged medication. The cinchona alkaloids are given after meals in order to lessen gastric irritation. The best means of administration is to give the drug in gelatin capsules. This obviates the necessity of masking the bitter taste, and insures rapid absorption of the chemical from the intestine. Pills and tablets should not be used unless the former are fresh and soft, and the latter have a coating which is readily soluble in the gastro-intestinal fluids. Frequently quinine is given in pills and tablets which are as hard as concrete and therefore it is unabsorbed and passed with the feces. For young children, quinine may have to be given in solution. The syrup of licorice and the aromatic syrup of eriodictyon are vehicles helpful for this purpose.

Whenever possible, the oral route of administration should be employed. It is safest, least disagreeable and permits sufficiently rapid and adequate absorption of the drug. Rectal instillations are unsatisfactory and often irritating. Intramuscular or subcutaneous injections are painful and may cause tissue injury, abscess or slough. Intravenous injection of quinine is to be reserved for certain emergencies as described under the therapy of malaria.

Therapeutic Uses

The most important therapeutic use of quinine is in *malaria.* This is discussed on page 921.

Analgesia and Antipyresis. Quinine in oral doses of 0.3 to 0.6 gram is employed for the relief of headache, myalgia, arthralgia, neuralgia, etc., and for reducing fevers. It has, therefore, the same general field of usefulness as the salicylates but is somewhat less effective. Repeated medication causes unpleasant symptoms of cinchonism.

Auricular Fibrillation, Auricular Flutter and Premature Systoles. Wenckebach's discovery of the action of quinine in auricular fibrillation soon led to the use of quinidine in this arrhythmia. Quinidine is much more effective than quinine and is therefore preferred for the therapy of auricular fibrillation, auricular flutter, and extrasystoles. Some physicians, however, still employ quinine hydrobromide for the treatment of extrasystoles. Others use the so-called "Wenckebach pills" which contain quinine, 0.1 gram and strychnine, 0.001 gram. It is probably the quinine which exerts the beneficial effect. Despite the fact that strychnine has no known pharmacodynamic action serviceable in treating extrasystoles, it is said by some to enhance the effect of quinidine (Carter and Traut, 1935). Quinine has also been employed to slow the tachycardia of hyperthyroidism.

Local Anesthesia. The local anesthetic uses of quinine solutions are discussed elsewhere (page 304). More efficient and safer local anesthetics than quinine are available and deserve preference.

Quinine as a Sclerosing Agent. Quinine is sometimes employed in the treatment of *varicose veins.* It acts by irritating the vascular endothelium and causing thrombosis. Quinine hydrochloride with urethane is the preferred preparation because it is neutral in solution. Marked cinchonism may occur and it is best to use not more than one cc of the commercial solutions at any one time. Tissue sloughs from extravasation as well as postobliterative sloughs occur, and the skin over the vein may become bronzed. Quinine cannot be considered to be the sclerosing agent of choice. Nevertheless, quinine and urea hydrochloride solution is sometimes preferred in the treatment of hemorrhoids, especially those which cannot be treated surgically. A five or ten per cent solution is injected in sufficient quantity to distend the hemorrhoid, the injection being made as far away as possible from the mucocutaneous junction. The treatment is said to be simple, effective and usually painless (Terrell, 1927).

Use of Quinine in Labor. Quinine is occasionally employed for initiating labor, as was described under the clinical use of oxytocics. It also enjoys some popularity as an abortifacient but is most unreliable in this regard.

Myotonia Congenita and Other Myopathies. Myotonia congenita, a rare myopathy of unknown etiology, is also called Thomsen's disease after the physician who first described it and in whose family it had existed for five generations. It is characterized by tonic spasm of skeletal muscles when voluntary movement is attempted. Both contraction and relaxation are slow. The myotonic electrical reaction of Erb is characteristic of this condition. In some cases of *myotonia atrophica* there may be an element of this same disorder of contraction. Pharmacologically, at least, myotonia congenita is the opposite of myasthenia gravis, and the drugs effective in one disorder aggravate the other. Quinine has been shown to cause dramatic improvement when given orally in myotonia congenita in a dose of 0.3 to 0.6 gram, repeated two or three times daily (Wolf, 1936; Smith, 1937; Kennedy and Wolf, 1938; Kolb, Harvey and Whitehill, 1938). The myotonic symptoms are quickly and sometimes entirely relieved. The electrical reactions also return to normal. The alkaloid is not curative and exerts its beneficial effect only as long as it is given. The mechanism of action of quinine on skeletal muscle has already been described.

It is of interest to note that quinine is also effective in obliterating the muscular rigidity in goats suffering from congenital myotonia (Kolb, 1938), a disease similar to that occurring in human beings. The nature of the abnormal muscle physiology in goats with congenital myotonia and the influence of various drugs upon the syndrome have been studied by Brown and Harvey (1939). The myotonic muscle appears to be in a state of incessant activity and exquisitely sensitive to mechanical stimulation. The isometric tension maximum attained by the myotonic muscle in response to a single maximal shock applied to its nerve is greatly in excess of that of the corresponding muscle from a normal animal. The time required for full relaxation after contraction is longer than normal. Tetanic stimulation of the motor nerve (frequencies of order of 50 per second) aggravates the myotonia, and the muscle remains tetanically contracted after the stimulation has stopped. This persisting contraction resembles the rigidity noted in Thomsen's disease following a sudden voluntary effort. Stimulation at a frequency of five per second causes a progressive diminution of the abnormal activity, a phenomenon reminiscent of the relief of myotonic symptoms in man by the rhythmic activity of mild exercise. The myotonic muscles are not abnormally sensitive to acetylcholine in that the amount of drug necessary to elicit a given tension maximum is approximately the same as for normal muscle. However, the duration of the response to a given dose is greatly prolonged. The myotonic muscle is abnormally sensitive to potassium ions, and responds with a prolonged contraction of considerable tension to an amount of potassium chloride which is ineffective in normal muscle. Poisoning of the muscle with curare and section and degeneration of the motor nerve do not modify the characteristic responses to mechanical stimulation or to potassium. Quinine, on the other hand, abolishes the abnormal sensitivity of the myotonic muscle to mechanical stimulation. Eserine does not enhance contraction of the myotonic muscle more than normal muscle. The responses of the abnormal muscle to various stimuli are accompanied by oscillatory action potentials and must therefore be viewed as asynchronous, tetanic contractions of muscle fibers. The abnormality resides in the muscle fiber itself and not in the neuromuscular transmitting apparatus.

In cases of *myotonia atrophica* (dystrophic myotonica) manifesting muscular dysfunction, quinine is sometimes effective but does not influence the muscular atrophy, cataracts, baldness, ovarian dysfunction, and testicular atrophy characterizing this disorder (Waring and coworkers, 1940).

Quinine can also be used as a *diagnostic test for myasthenia gravis* (page 386). Subclinical symptoms become obvious after quinine, and if prostigmine is then given these symptoms improve quickly. In *dystonia musculorum deformans,* Hassin (1939) has reported favorably on the use of quinine for symptomatic therapy of the uncontrollable movements. He has also obtained promising results with quinine in so-called *spasmodic torticollis* (torsion spasm), viewed by some as a partial manifestation of dystonia.

Miscellaneous Uses of Quinine. Quinine is used as a stomachic. Appetite may be improved by taking a small amount of a quinine-containing mixture, such as the *Compound Tincture of Cinchona,* four cc, or *Elixir of Iron, Quinine and Strychnine,* four cc. The action is due to the bitter taste and mild irritant action of the quinine. If the dose is too large, gastric secretion may be inhibited. In the treatment of rectal *constipation,* quinine is sometimes used in suppositories or in solution as small enemata. The mechanism of action is probably rectal irritation, because quinine taken orally does not increase bowel activity. As a *contraceptive* agent, quinine has been employed in jellies and douches but its spermatocidal efficacy is low and unreliable (page 675). In *hyperthyroidism,* quinine was formerly used to depress the metabolic rate. The tolerance to the drug shown by thyrotoxic patients has never been adequately explained. The tachycardia of hyperthyroidism may be slowed by the myocardial action of the alkaloid. Certain cases of *erythroblastic anemia* of infants and *sickle cell anemia* have been treated with quinine with occasional success, the rationale being that some cases may be due to congenital malaria. The use of quinine in *"hair tonics"* is entirely irrational and has caused severe skin reactions in hypersensitive individuals.

HYDROCUPREINES

A large number of hydrocupreine derivatives have been prepared and the study of their specific antiseptic properties against bacteria is a major field of chemotherapy. Inasmuch as the clinical applicability of these discoveries is restricted, only the most important features of the hydrocupreine compounds will be presented.

The structural formula of cupreine is given on page 905. *Hydrocupreine* results from reduction of the vinyl group in cupreine to CH_2CH_3. The substitution of alkyl groups in the side-chain of the quinoline ring gives rise to a series of compounds which often have distinctive antiseptic properties. Some of these have a high bactericidal potency even in the presence of proteins, and are effective upon systemic administration. From time to time enthusiastic reports have appeared concerning the use of one or another of the hydrocupreines in bacterial infections but more extensive study has shown them to be unsuitable. The main objection is their toxicity. The drug which has been most frequently tested clinically, *ethylhydrocupreine,* is specifically toxic to the optic nerve.

Ethylhydrocupreine (Optochin). Ethylhydrocupreine is a light yellow, bitter powder. It is usually employed as the hydrochloride salt (U.S.P.). It has the same chemical constitution as quinine except that there is an ethoxy instead of a methoxy side-chain and the vinyl group is reduced. It differs in action from quinine mainly in its greater pneumococcicidal efficacy, but also in being less antipyretic, and more toxic to the heart. The studies of Morgenroth (1918) were confirmed by many others and established that extremely high dilutions of ethylhydrocupreine were capable of killing a number of strains of pneumococci even in the presence of serum. Although the experimental results were excellent, the clinical experiences were discouraging. The drug was found to cause blindness, and deaths resulted from its intravenous use. In some series, the incidence of amblyopia from ethylhydrocupreine reached 10 per cent. The visual disturbances described under quinine were noted but occurred in a more severe form. Furthermore, the clinical results were disappointing in pneumococcal pneumonia (Moore and Chesney, 1918). The systemic use of ethylhydrocupreine is therefore dangerous and unsatisfactory, and is not advised. Ethylhydrocupreine, however, may be used locally as an ointment or solution (one to two per cent strength) in *pneumococcal eye infections.* It has also been applied topically as a one per cent solution in *pneumococcal stomatitis* in infants.

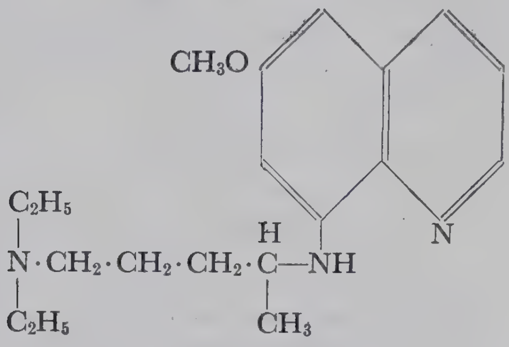
Investigation continues in the search for nontoxic but effective hydrocupreine derivatives for use in human pneumococcal infections (Maclachlan and coworkers, 1937, 1939; Dawson and coworkers, 1937; Butler and coworkers, 1937; Bracken and associates, 1940; Maclachlan, 1940), and the most promising compound appears to be hydroxyethylapocupreine.

Two of the higher homologues of hydrocupreine which have received considerable bacteriological study are *isoamylhydrocupreine* (*eucupine*) *and isooctylhydrocupreine* (*vuzine*). Inasmuch as these drugs are not used clinically, their description is omitted. Their interesting properties have been reviewed by von Oettingen (1933).

PLASMOCHIN

Plasmochin (plasmoquine) was synthesized by Schulemann, Schönhöfer and Wingler on the basis of experiences with methylene blue, and introduced into medicine for its antimalarial action by Mühlens (1926).

Chemistry and Preparations. The synthesis of quinoline compounds of this type was suggested by the fact that methylene blue is somewhat plasmodicidal, and the introduction of aminoalkyl groups was found to enhance this property. *Plasmochin* is a quinoline derivative, 6 methoxy-8-(α-methyl-δ-diethylaminobutyl) aminoquinoline, and has the following structural formula:



Plasmochin

The drug is a tasteless white powder available as the hydrochloride salt in pills or capsules. It is also dispensed in tablets in combination with quinine sulfate in fixed doses.

Pharmacological Actions. In avian malaria, plasmochin appears to be approximately sixty times as effective as quinine. Plasmochin is particularly interesting because of the specific toxicity it manifests toward the gametocytes of all forms of plasmodia. Whereas full therapeutic doses of quinine in man do not cause the disappearance of the sexual forms even after three weeks, plasmochin effects their elimination in a few days so that the blood of treated patients is no longer infectious for the mosquito. Plasmochin also has some action against the asexual forms of the malarial organism. It is moderately effective against benign tertian and quartan malaria, and has been shown to prevent inoculation malaria. It fails, however, to destroy the parasites causing the symptoms of malignant tertian or estivoautumnal malaria. The exact means by which this chemical attacks the plasmodium and why the action is selective for the sexual forms are problems which require further investigation.

Fate and Excretion. Variable amounts of plasmochin are destroyed in the body, and the remainder is excreted in the urine. This excretion is quite slow, and cumulative toxicity can result from continued medication.

Toxic Effects. The margin of safety of plasmochin is rather narrow. The commonest effect of full doses is cyanosis due to *methemoglobinemia*. This pigment change can also be demonstrated *in vitro*. The functional anemia resulting from the methemoglobinemia causes weakness, vertigo and prostration. The blood cells may hemolyze and hemoglobinuria and jaundice may then appear. A *lymphocytic leukocytosis* may be induced by plasmochin. The drug is also toxic to the *heart* and tachycardia, extrasystoles and other arrhythmias may result. Sudden cardiac collapse may occasionally ensue. In some patients, a pronounced *mydriasis* may develop. The commonest *gastro-intestinal symptoms* following plasmochin are nausea, vomiting, epigastric pain and diarrhea. The *liver* and *spleen* may become tender, and the *blood sugar* may fall. Central necrosis of the liver is a major finding in fatal cases. Somnolence and coma develop after severe intoxication. Cyanosis should be the signal for discontinuation of medication. Milder side-actions can be prevented by giving the drug after meals.

Feeble patients and those with heart, kidney or liver disease are more susceptible to poisoning by plasmochin and the drug is contraindicated in such individuals. Marked anemia also appears to predispose to methemoglobin formation. Children are more tolerant to the drug than adults. Full doses of plasmochin are too toxic to be given unless the patient is under close observation, preferably in a hospital. Some authorities feel that plasmochin should be used only in small doses combined with quinine. They claim that these small doses (20 mgm per day for an average adult) are sufficient to destroy the sexual forms and that quinine should be used to supplement the treatment.

Advantages and Status. Plasmochin has the distinct advantage over quinine of destroying the sexual forms of the parasite. This is important from the public health standpoint. Cinchonism is not produced and plasmochin can thus be used in patients sensitive to the cinchona alkaloids. The lack of an oxytocic effect allows the drug to be employed in pregnant women if quinine is contraindicated. Similarly, it may be used in cases of blackwater fever if quinine proves too toxic.

Plasmochin is to be viewed as a valuable adjuvant to quinine rather than as a substitute for the latter. When it is used alone in full doses, unpleasant reactions are common and relapses are frequent. It is completely ineffective in malignant subtertian malaria. By combining plasmochin and quinine, the dose and toxicity of each can be correspondingly reduced and both the schizonts and gametocytes attacked. In this way, the disease and its transmission through carriers are better controlled. When combined with quinine for the therapy of acute attacks, or when used in alternation with atabrine, plasmochin considerably reduces the relapse rate, particularly in cases of benign tertian and quartan malaria and in some cases of malignant tertian malaria. For simple clinical prophylaxis, however, it is doubtful whether plasmochin alone has value. The value of plasmochin in comparison with atabrine and quinine in various forms of malaria is summarized in Table 46.

Doses and Administration. The full oral dose of plasmochin for adults is 60 mgm per day, usually given in three divided doses of 20 mgm each. Medication should not be continued, without rest periods, for more than 14 consecutive days. Toxic effects appear in direct proportion to the length of time the drug is used. It is not recommended to use plasmochin alone in patients who can tolerate combined quinine and plasmochin therapy, because full doses of plasmochin are likely to prove toxic. Deaths have resulted from 80 mgm of plasmochin a day. The exact dose and form of administration of the drug for young children have not been determined.

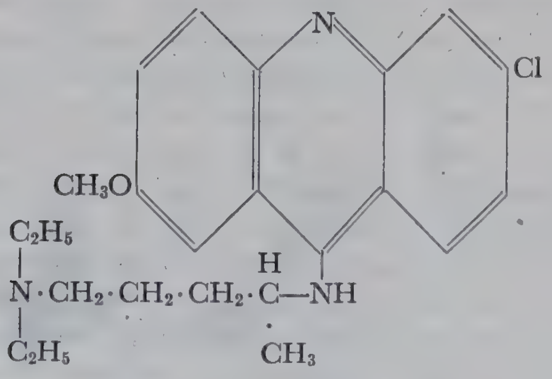
When the two drugs are given together, the daily dose of quinine is 1.3 grams and that of plasmochin is 20 to 40 mgm. These amounts can be given in divided portions. Plasmochin in the daily dose of 10 to 20 mgm appears to be an effective and safe prophylactic against the transmission of the plasmodia to mosquitoes. "Plasmochin compound" is a preparation on the market containing in each tablet 0.01 gram of plasmochin hydrochloride and 0.12 gram of quinine sulfate. Another preparation (chinoplasmin) is available in which five mgm of plasmochin are combined with 0.16 gram of quinine.

Plasmochin has also been administered with atabrine, but there is abundant evidence to indicate that toxic reactions are increased by such medication. These reactions can be avoided and the advantages of dual medication retained by giving a course of atabrine (0.3 gram per day) for the acute attack and following this with plasmochin (20 mgm per day) for five days. This procedure lessens the rate of relapse and kills gametocytes.

ATABRINE

Atabrine (atebrine) was introduced for malariotherapy by Schulemann (1930). The drug was synthesized by Mauss and Mietzch on the basis of the clinical results obtained with plasmochin. It is said that over 12,000 compounds were systematically prepared and tested in discovering plasmochin and atabrine.

Chemistry. Atabrine, 2-methoxy-6-chlor-9-(α-methyl-δ-diethylaminobutyl) aminoacridine, is a substituted alkyl amino derivative of acridine. The side-chain in this compound is the same as that in plasmochin. Substitutions can apparently be made in this side-chain without seriously altering the antiplasmodial activity, but this does not seem to be true for plasmochin. The structural formula is as follows:



Atabrine

Atabrine is a yellow bitter powder. It is usually marketed as the dihydrochloride salt in yellow tablets, or as the powder which dissolves in water to the extent of three per cent to form a neutral fluorescent solution. The drug is not official and is not included in N.N.R.

Pharmacological Actions. In bird malaria, atabrine is much less effective (15 times) than plasmochin and also less toxic; but it is more active than quinine. In contrast to plasmochin but similar to quinine, the drug affects mainly the asexual forms. Thus it is curative in malaria in the same sense as quinine, but does not prevent the patient's blood from remaining infectious for mosquitoes. The potency of atabrine as compared with quinine in human malaria has been the subject of considerable study. There is little evidence that it is superior to the cinchona alkaloids, except in the treatment of malignant subtertian malaria where it appears to be more effective than quinine.

The mechanism of action of atabrine in malaria is not understood. While it is tempting to assume that this chemical is directly plasmodicidal, there is no more evidence for this than in the case of quinine. The drug can be detected in the parasite due to the brilliant greenish fluorescence it shows in ultraviolet light.

Absorption, Fate and Excretion. Atabrine is absorbed readily from the gastro-intestinal tract. It is stored especially in the liver, spleen and reticuloendothelial system where it can be detected by fluorescent analysis. It is excreted slowly by the kidneys and appears in the urine. It is also excreted in the bile, but this fraction is again absorbed by the intestinal tract. This may account in part for the slow excretion of the drug. Atabrine usually appears in the urine within a few hours after it is administered, but it is still excreted for two or three weeks after the drug is discontinued. Urine containing the chemical turns a bright yellow upon the addition of acid. The color is best detected by acidifying the urine with a few drops of acetic acid, heating, and looking down through the solution against a black background. Atabrine is also excreted in the milk.

Toxic Effects. The toxicity of atabrine is apparently low and the margin of safety therefore good (Martin and associates, 1939; Clark and associates, 1939). Doses larger than those ordinarily used may cause gastro-intestinal disturbances such as nausea, vomiting, and diarrhea. A few patients may complain of abdominal pain from therapeutic amounts. Headache and anorexia are occasionally noted.

The skin turns yellow in about 50 per cent of patients receiving atabrine. The color usually disappears from the skin about ten to fifteen days after the drug is stopped, but may remain from many weeks to four months or longer. It should not be mistaken for jaundice from which it can readily be differentiated by testing for hyperbilirubinemia. All tissues including the central nervous system are pigmented by the drug. The sweat, tears, and nasal secretions may also be colored a deep yellow. Apparently no harm results from this. The discoloration of the skin is diffuse, but is most prominent on the dorsum of the arms, hands, and feet and in the folds of the skin. The face and forehead are also pigmented and a golden ring may form around the mouth. No dermatitis or change in skin texture occurs. The sclerae remain clear, a distinguishing feature from jaundice (Schechter and Taylor, 1936).

Transient psychoses have been noted. In some individuals, this may take the form of a profound depression; in others, a delirium or mania may occur and develop into stupor or coma lasting many days. It has been suggested that these reactions may be a manifestation of idiosyncrasy to the drug. There are no contraindications to the use of atabrine except perhaps impaired renal or hepatic function.

Advantages and Status. In proper doses, atabrine is well tolerated and more pleasant to take than quinine. It does not cause cinchonism and lacks the intense bitter taste of cinchona alkaloids. The drug also has no oxytocic action and can therefore be used in late pregnancy when quinine may be contraindicated. It may also be preferred in cases of blackwater fever. The short course of treatment is also a definite advantage.

Although atabrine is still too new to be given a final clinical appraisal, it would appear to be at least as effective as quinine in the three forms of malaria. The opinion of many workers that this chemical is more efficient than quinine in curing malaria and preventing relapses must await further confirmation. There is reason for believing it superior in the treatment of malignant or subtertian malaria. While therapeutic doses affect mainly the schizonts, the gametocytes of the benign tertian (*P. vivax*) and quartan (*P. malariae*) forms of the disease are also inhibited by atabrine. Those of malignant tertian malaria (*P. falciparum*) are not destroyed by the drug. When used instead of quinine in the acute malarial attack, atabrine apparently decreases the rate of relapse. If relapse occurs, it appears later after the last dose of atabrine than is the case with quinine. This is probably due to the slower rate of atabrine excretion from the body. The value of atabrine in comparison with plasmochin and quinine in various forms of malaria is summarized in Table 46.

Doses and Administration. The usual dose of atabrine for adults is 0.1 gram, given orally in capsules or tablets and repeated three or four times daily. A course of treatment lasts from five to eight days and this should not be repeated for several weeks. Gastro-intestinal irritation is prevented by taking atabrine after meals. Children seem to require more than their age alone would indicate, and can receive the adult dose when they are eight years old. The exact dose and form of administration of atabrine for children, however, have not been determined.

For purposes of prophylaxis, 0.2 gram of atabrine may be given on two consecutive days of each week. This is apparently more efficient than 0.4 gram of quinine given daily. In the Fourth General Report (1937) already referred to, the following figures, taken from experiments meeting the League of Nations requirements, are advanced without comment: 149 relapses among 804 patients given quinine during the interepidemic observation period; 143 relapses among 2,142 atabrine-treated patients. Atabrine can also be combined for prophylactic purposes with plasmochin, but this increases the toxicity and expense. The opinion that atabrine is superior to quinine as a preventive of malaria has been challenged by Clark and Komp (1937) on the basis of their careful studies in Panama. In contrast to the Panama experience, however, the results of Bastianelli (1937) working in Sardinia showed that 0.2 gram of atabrine given twice weekly was nontoxic, practically eliminated benign tertian malaria, and greatly decreased the incidence of malignant tertian cases during epidemic periods.

The length of time during which atabrine in prophylactic doses can be continued without danger is unknown, but apparently it can be given for six months without toxic effects, although the skin may turn yellow. There is some reason to believe that if malaria develops in a patient receiving atabrine, it may be clinically more severe. Also it has been noted that in some patients who received the drug *after* the disease had developed, the symptoms may be aggravated for the first few hours.

In severe malaria when intravenous medication may be required, atabrine can be given in a dose not exceeding 0.1 gram, injected slowly in 10 cc of solution and not repeated more than twice within a 24 hour period. Atabrine may also be administered intramuscularly (0.2 gram in 10 cc of solution). The drug is rapidly absorbed, and this is the parenteral route which is preferred. In pernicious malaria other than blackwater fever, many prefer intravenous quinine to intravenous atabrine.

The combination of atabrine and plasmochin is favored by some as decreasing the incidence of relapse, but there is evidence that such therapy increases the number and severity of toxic effects. For this reason, other workers prefer to alternate courses of atabrine with those of plasmochin, with or without a rest period intervening. Direct and constant medical supervision should always accompany the use of atabrine.

CHEMOTHERAPY OF MALARIA

Malaria is a very ancient disease and has been a determining factor in the progress of civilization. Its ravages have decimated entire populations, checkmated invading armies and balked attempts at empire building. It is a matter of history that the French were prevented by malaria from completing the canal through Panama.

Malaria attacks several hundred million people annually. Next to helminthiasis, it has the greatest incidence of any disease. It has been estimated that three million people die annually from malaria. It is erroneous to believe that malaria occurs only in the tropics for the disease is worldwide in distribution. This holds true particularly for the tertian form which is the prevailing type in the temperate zones. Even the main tropical form (malignant subtertian) occurs in the Southern United States in the Summer and early Autumn.

Biology of the Malarial Infection. Laveran discovered the parasite causing malaria in 1880, and in 1898 Ross showed that the *anopheles* mosquito was the vector. Yet the infectious nature of the disease and the etiotropic action of quinine had been postulated several years before by Binz. Indeed, it appears that even the ancients had associated the disease with mosquitoes.

Inasmuch as the specificity of drugs in the treatment of malaria depends on the type of infecting parasite, it is essential briefly to review at this point the nature of the malarial infection.

Malaria is a protozoan disease caused by four species of *plasmodia,* which form one of the families of the suborder *hemosporidia.* The latter are *sporozoa* which have become adapted to an asexual cyclical existence in circulating red blood cells of certain vertebrates and to a sexual sojourn in the anopheline species of mosquito.

The life cycle and reproduction of the plasmodia are as follows: Man is the intermediate host in which the parasite completes its *asexual* (endogenous) cycle and reproduces by a process of *schizogony.* The anopheles mosquito is the vector and definitive host in which the *sexual* (exogenous) cycle is completed and reproduction accomplished by *sporogony.* In man, the plasmodium lives as an ameboid and pigmented parasite in or on the surface of red blood corpuscles which are eventually destroyed by the growth and division of the parasites. It is first called a *trophozoite* as it attaches itself to the red cell. Upon the division of the nuclear chromatin material, the *schizont* stage is reached. When the red blood corpuscle bursts, numerous small bodies called *merozoites* are liberated into the blood stream. It is this periodic breaking of red cells which causes the typical attacks of rigor so characteristic of malaria. The *fever* which follows the chill is due to the liberated foreign protein and cell products. In a single febrile paroxysm, as many as one-fifth of the circulating red blood cells may be destroyed. The free-swimming merozoites again attach themselves to blood corpuscles to become trophozoites and to repeat once more the process of schizogony. After several cycles of the sort described above, and especially when growth conditions are unfavorable due to medication or developing immunity, some of the merozoites invading red blood cells fail to follow the asexual pattern of reproduction. They differentiate into male and female parasites known as *gametocytes*. These gametocytes grow until they fill and break out of the red blood cells, but they do not divide again in man and cause no symptoms. The gametocytes remain free in the blood of human "carriers" until they are taken up by a mosquito.

It is the person who carries gametocytes in his circulation who is infective for mosquitoes. The latter take up the parasite in the course of obtaining a blood meal from man. In the mosquito, the sexual cycle and reproduction by sporogony are completed. Fertilization occurs in the insect's stomach after the sexual forms have undergone further differentiation. The fertilized forms or zygotes complete more changes and after multiplication and migration they are distributed as *sporozoites* in all the tissues of the mosquito but especially in the salivary gland cells and ducts. When the mosquito bites man, the sporozoites in the saliva are liberated into the victim's blood, invade the red blood cells and once more become trophozoites. Thus, the asexual cycle, which is the basis of human malaria, begins again.

Mechanism of Action of Quinine in Malaria. Although quinine has been employed for three centuries in the treatment of malaria, the basis for its use is as empirical today as it was when the Countess of Chinchon was given a decoction of cinchona bark. While it is tempting to believe that quinine, a protoplasmic poison, acts by a direct plasmodicidal effect, the evidence far from substantiates such an assumption. Experiments in this field are handicapped by the fact that the cultivation of plasmodia *in vitro* is a difficult matter. Cultures last only for a few generations and the asexual forms cannot be grown.

The reason that quinine cannot be accepted at present as directly plasmodicidal is that much higher concentrations of the drug are needed to kill the parasite *in vitro* than are ever obtained in man from therapeutic doses. Indeed, many other substances ineffective clinically in malaria can be shown to kill the plasmodia in the test tube in concentrations no higher than are needed for quinine. Many studies have indicated that a period of incubation with a 1:10,000 solution of quinine is required to arrest the motility of plasmodia and to alter their growth and staining properties. It is also established that the amount of quinine in the blood of a patient under treatment is only 1:150,000 to 1:100,000.

The real proof of plasmodicidal action rests on a demonstration of loss of infectiousness of the parasite for man after contact with specific drugs. The advent of malarial therapy for general paresis provided a means for the performance of this crucial test. The experiments of Kirschbaum (1923) may be quoted in this connection. He mixed blood from patients with tertian malaria with an equal volume of 1:5000 quinine hydrochloride in isotonic sodium chloride or dextrose solution. Even after incubation at 38 C. for five to 24 hours, the blood remained infectious as tested by injections into man. It was also demonstrated that an incubation period of over 24 hours was needed with these high concentrations before infectiousness was destroyed (Mühlens and Kirschbaum, 1924). These experiments were later confirmed by other investigators. Another crucial type of study was made by James, Nicol and Shute (1927) when they teased sporozoites from the salivary glands of infected mosquitoes and showed that the injection of these parasites into man caused malaria. They then placed the mosquitoes in blood serum containing quinine bisulfate in 1:5000 strength, and dissected out the salivary glands. After an incubation period of fifteen minutes, the serum was injected subcutaneously into man and caused a typical malarial paroxysm with plasmodia demonstrable in the patient's blood. Thus, a high concentration of quinine was incapable of killing sporozoites within the incubation period used. These experiments cast considerable doubt on the theory of a direct lethal action of quinine on malarial plasmodia.

It was therefore necessary to seek other explanations of quinine action in malaria, and these have been forthcoming in abundance. The theory has been advanced that quinine actually kills some plasmodia, thus releasing antigen which stimulates the body to form antibody against the remaining parasites (Yorke and Macfie, 1924). An attractive theory growing out of the known propensity of quinine for producing surface films was that the drug prevented the entrance of the parasite into red blood cells and in this way halted the malarial cycle. The quinine was thought to be concentrated on the surface of the corpuscles and either made these impervious to the merozoites or interfered with the development of parasites already in the cells. Neither the amount of quinine found in the blood even after intravenous injection nor the distribution partition coefficient between cells and serum supports this contention. While it may be true that only those quinine derivatives that are antimalarial can penetrate red cells (Hegner and coworkers, 1928), this does not necessarily indicate an intracorpuscular site of action of quinine. Many other theories have been advanced including those which postulate that quinine stimulates the production of immune bodies, enhances phagocytosis by monocytes, decreases the plasmodial resistance to lytic agents in the serum, or increases the red cell permeability to such lysins. Furthermore, the claim that quinine acts through an intermediate product is not supported by the evidence because all the recognized degradation products have been tested and found to be less antimalarial than quinine itself.

Regardless of the mechanism of its action, quinine cures the acute symptoms of malaria by depressing multiplication of plasmodia in the body and stimulating some of the parasites to change to the sexual form which cannot cause the disease in man. The term "plasmodicidal" is employed in this discussion without implying particular means by which the drug brings about the death of the parasite.

Treatment of Malaria. The treatment of malaria is complicated by the fact that the different species of plasmodia do not respond with the same readiness to drug therapy, that the gametocytes and schizonts manifest different chemotropisms, that individuals vary in their responses to quinine, and that the chronicity of the infection is an important consideration. Early infections, for example, are, as a rule, very easy to cure compared with chronic malaria. One should hasten to add that by "cure" of malaria is usually meant the immediate control of symptoms. Relapses are frequent and difficult to prevent. Early and intensive treatment affords the best chance to obtain a complete cure including prevention of relapses. In order to treat malaria intelligently, the species of infecting plasmodium must be ascertained because the efficacy of drugs varies with the type of parasite. The value of quinine in comparison with plasmochin and atabrine in the therapy and prophylaxis of malaria is summarized in Table 46.

The *benign tertian* form of malaria is caused by the plasmodium *vivax* which has a reproduction cycle of 48 hours. This disease shows an excellent immediate response to quinine but relapses are frequent. Despite the best type of treatment, one can expect a relapse rate of five to 10 per cent. The *malignant, subtertian or estivo-autumnal* form of malaria is due to the plasmodium *falciparum* which requires 36 to 48 hours for schizogony. This disease is difficult to cure because many of the parasites remain in the capillaries of internal organs, especially the spleen and bone marrow, where they may not be readily accessible to the administered quinine. This form is often difficult to diagnose and causes fatal epidemics. Once the patient is cured, however, there are few relapses. There is evidence to show that quinine is more potent against the schizonts of plasmodium falciparum than those of plasmodium vivax, whereas the opposite is true for the gametocytes. Once quinine reaches a sufficiently high concentration in patients with malignant tertian malaria, the disease responds very well. This has been correlated with the higher concentration of the drug in capillaries and the tendency of plasmodium falciparum to sporulate in these small vessels. The *quartan* type of malaria is caused by the plasmodium *malariae* which has a reproduction cycle of 72 hours. The success of therapy is intermediate between that obtained in the two forms

TABLE 46

CLINICAL AND LABORATORY DATA ON EFFICACY OF ANTIMALARIALS *

		QUININE	ATABRINE	PLASMOCHIN	
TROPHOZOITES	P.v. and P.m.	Infection effectively controlled by a mean daily dose of 1.0 gram given for 5 to 7 days.	A daily dose of 0.3 gram is slightly more rapid in action than 1.0 gram of quinine and continues effective longer after the end of medication.	Active to some extent especially on P.m.	Combination with quinine gives better results than quinine alone.
	P.f.	Minimal daily dose of 1.0 gram required, often 2.0 gram dose needed.	Same as above; but conclusions rendered difficult, due to different strains. Trophozoites disappear from peripheral blood after fourth dose in 90% of cases.	Efficacy is almost nil.	
GAMETOCYTES	P.v. and P.m.	Effective on young forms and fully developed gametocytes.	Slightly more effective than quinine for gametocytes already in the blood.	Acts against the three species, and especially P.f. which is unaffected by quinine or atabrine. Even minimal doses of 20 mgm per day devitalize gametocytes of P.f. and reduce their number.	
	P.f.	Only slight gametocidal action on adult forms, but impedes formation of sexual forms of this species.	No gametocidal action.		
Clinical Symptoms of the Acute Attack		Suitably and readily effective in malaria due to P.v. and P.m. Somewhat longer time needed for control of P.f.	Very marked action on all forms and especially in malaria due to P.f.; but not in all of the latter. Some malariologists prefer quinine for the first few days in malignant tertian cases, and then continue therapy with atabrine.	No indication for or advantage in using this drug alone for the acute attack of any form of malarial infection.	
Relapse Rate		Even when quinine is given in 1.0 gram daily doses for the acute attack, the relapse rate is sometimes still as high as 50% in malaria due to P.v. and P.m.	Relapse rate is apparently less than with quinine especially in cases due to P.v. and some strains of P.f.	Given with or after quinine or atabrine, this drug causes a marked decrease in relapses in the three forms of malaria.	
Splenomegaly		Very efficacious if the drug is used in each succeeding attack.	Slower decrease in size of spleen than with quinine but effect is more lasting.	Status of plasmochin alone is unknown, either for therapy or prophylaxis.	
Effect of Therapy on Patient's Health.		Not toxic as a rule if limited to the number of days strictly necessary. No reason for thinking the drug hinders the body's immune processes. Ill effects may occur if quinine therapy is continued unreasonably long.	Yellow skin. Fairly safe and well tolerated in proper doses. Effects on body's defenses and immune processes are unknown.	A daily dose of 20 mgm is not injurious. Larger doses may cause toxic effects.	

P.v. = Plasmodium vivax
P.m. = Plasmodium malariae
P.f. = Plasmodium falciparum

* [illegible] published in the conclusions of the Fourth General Report of the Malarial Commission of the League of Nations (1937). (After Goodman, 1940)

cited. Mixed infection can also occur due to two species of infecting plasmodia. The rare plasmodium *ovale* is not encountered in the temperate zones. It has a reproduction cycle of 48 hours, causes a fairly mild form of malaria, and yields satisfactorily to quinine.

Quinine is the drug of choice in the treatment of acute malaria. In certain parts of the world, especially the tropics, the cost of malarial therapy is a primary consideration in the choice of drugs, and many relatively inexpensive mixtures of cinchona alkaloids are employed. In the United States, however, quinine salts are nearly always prescribed. In 1919, the National Malaria Committee adopted the following routine of therapy which is still used. The patient is given 0.65 gram of quinine orally two or three times daily for three of four days or until acute symptoms disappear. Then a dose of 0.65 gram is given every night for eight weeks. With this therapy about 90 to 95 per cent of cases will be permanently cured. In order to prevent the five to ten per cent rate of relapse, many practitioners continue the three daily doses until the parasites are gone from the blood and the single nightly dose is maintained for twelve weeks instead of eight. The dose for children is proportional to age.

There are many who are disappointed with this routine treatment and point out that it is expensive, requires coercion, and does not prevent relapses. They consider that quinine should be used only for the control of symptoms of the acute attack, and not repeated unless a relapse occurs (*see* the Third General Report of the Malarial Commission of the Health Organization of the League of Nations, 1933). The Fourth General Report (1937, page 920) of the Malarial Commission voiced a similar view as follows: "Unfortunately there are still too many cases, in private practice, that require only a seven-day, or, at most, a ten-day course with *ordinary* therapeutic doses, but are positively drenched with specific drugs for more or less lengthy periods." This view, however, has been vigorously criticized, and it appears that the standard therapy should be employed if the patient can be induced to follow it properly.

The *time of administration* of the quinine in relation to the fever cycle once received considerable attention. There are still those who contend that the drug should be given when the acute paroxysm is declining because at that time there are free-swimming merozoites in the blood. It is immaterial, however, in what part of the cycle quinine is given because the parasite in all stages is apparently susceptible as long as a sufficient quantity of the drug is administered.

If gametocytes are also present in the blood, one should give plasmochin in a dose of 10 mgm three times daily for five or six days, during which period quinine should not be discontinued. This can be done after the acute symptoms have subsided, and serves the purpose of killing the sexual forms which render the patient infective for mosquitoes.

The *route of administration* of quinine in malaria is oral whenever possible. All the more soluble quinine salts seem to be equally effective. The bisulfate salt is commonly employed because of its higher solubility, but the dose should be increased one-quarter because of the lower alkaloidal content. Quinine is occasionally given parenterally. If the patient is moribund, as in cerebral malaria, or if vomiting and diarrhea prevent retention of oral quinine, intravenous injections can be given. These are dangerous, however, and should be reserved for emergency. The concentration of quinine obtained in the blood falls very quickly to the levels obtained by the oral route. The dihydrochloride is preferred for intravenous use because of its high solubility, and solutions can be sterilized by boiling. It is injected very slowly in the dose of 0.65 gram in 10 to 20 cc of physiological saline solution, or it may be dissolved in 100 cc of saline solution and given by gravity. This dose should not be repeated more than three times in 24 hours. Care is needed to prevent extravasation. A marked temporary *fall in blood pressure* is common and this may be serious in a patient with an impaired cardiovascular system. Cinchonism is the rule with this route of quinine administration, and occurs within ten minutes. It subsides gradually and is rarely serious. If cardiovascular collapse occurs following the injection, epinephrine may be given. The oral route should be resumed as soon as possible after the emergency is over.

Intramuscular administration of quinine so commonly causes abscesses that it should not be employed. The *rectal route* is not useful because quinine irritates the mucosa and the solutions are not retained.

Prophylaxis of Malaria. The prophylaxis of malaria is an extremely important public health problem which involves the extermination of mosquitoes, the prevention of human bites from species transmitting the disease, and the destruction of the sexual forms of the parasite in man. It is only the last-named procedure which comes under the province of pharmacotherapy. There is no drug which is markedly specific in preventing malaria. Quinine does not prevent one from becoming infected with the parasite, because an individual bitten by an infected mosquito will be inoculated with sporozoites. The drug merely keeps the plasmodia at such a low level of multiplication in the body that clinical symptoms do not develop. Quinine also causes the organisms to change to the sexual form by making their environment unfavorable. The gametocytes are incapable of causing clinical symptoms. When quinine is stopped, the disease may appear. *Quinine therefore prevents the disease but not the infection.* No drug is known which will effect a true prophylaxis of malaria in the sense that sporozoites are killed before they are able to continue their life cycle in the human host. It has not yet been shown that quinine or any of the synthetic drugs act on sporozoites rather than schizogenic forms of the parasite in the red blood cells. There is little question that the best hope of eradicating the disease lies in the prompt and effective treatment of the initial infection, for it is at this time that the plasmodia are most easily destroyed in the body, and gametocytes have no opportunity to develop. Craig and Faust (1937) summarized this point by saying, "It is undoubtedly true that if every initial malarial infection were properly treated, malaria would cease to exist, as mosquitoes could not become infected."

The prevention of symptoms in persons residing in malarial districts still rests upon the use of quinine. It is definitely established that the poor results reported in some quarters are due to the fact that the quinine was not actually taken by the patients. "Quinine resistance" in man probably does not occur, because once the quinine is swallowed and retained any such theoretical resistance quickly vanishes. The now familiar story of the experience of the French Army in Macedonia may be cited as one of numerous similar examples (Sergent and Sergent, 1932). In 1916, quinine was provided to the soldiers but its use was not enforced. Urine tests showed that only 15 per cent took the drug. The incidence of malaria was 2000 cases per division. In 1918, quinine prophylaxis was enforced and urine tests showed that 90 per cent of the soldiers took the drug. The rate of infection dropped to 125 cases per division.

Quinine in Prophylaxis. Quinine is given for prophylaxis in the adult oral dose of 0.5 to 0.65 gram daily. Mild cinchonism may occur but usually either disappears or ceases to be annoying. This prophylaxis can be continued for years without apparent harm, without producing "quinine fastness," and without impairing the efficacy of the drug if the acute disease should occur. Some workers advise the intermittent method of taking quinine on certain fixed days of the week, but most follow the continuous daily dose system (Italian method). In districts where the risk of infection is not great, the use of quinine perhaps should be reserved for treatment of the disease rather than its prevention. Quinine is still the most valuable drug for malarial prophylaxis due to its low toxicity and the fact that careful medical supervision is not required.

The *malarial carrier* should also be treated, because he harbors in his blood the sexual forms which may infect mosquitoes. Plasmochin is the drug of choice and its use and dose are described elsewhere.

Other Measures Employed in Malaria. In addition to specific therapy with quinine or the newer synthetics, the malarial patient must receive proper rest, sedation and nourishment. The salicylates aid in controlling the discomfort of headache and muscle pains. Ice bags or alcohol sponges will assist during the stage of fever. The *anemia* responds very well to iron preparations. The fluid intake must be maintained and electrolytes supplied if there is vomiting or diarrhea. In *pernicious malaria,* quinine must be administered without delay and it is here that its intravenous use is especially valid. The efficacy of arsphenamine or other organic arsenicals in malaria is unsettled, and the plasmodicidal value of these compounds has been questioned.

Blackwater Fever. This type of malaria, which is one form of pernicious malaria, is also called hemoglobinuric fever. Its etiology is unknown but the majority of workers agree that it is most often associated with malignant tertian malaria due to the plasmodium falciparum. Others claim it is a neglected form of chronic malaria or due to a coincidental bartonella infection. The death rate is very high (25 per cent) and the symptoms are those of a severe acute hemolytic crisis with injury to the kidneys and anuria. Transfusions and alkali therapy have been found helpful in maintaining renal function and combating acidosis, and abundant fluids and electrolytes are naturally indicated, because shock is present and must be treated (Wakeman and coworkers, 1932). Although the early and proper use of quinine in acute malaria will prevent blackwater fever, once the patient is predisposed to hemoglobinuria, the drug may precipitate or aggravate the syndrome. Quinine has been displaced by atabrine in many quarters for the specific therapy of hemoglobinuric fever. Whether atabrine or plasmochin can cause blackwater fever is still a moot question (Fourth General Report of the Malarial Commission, 1937). Plasmochin at least should be suspected of causing attacks because of its methemoglobin-forming property.

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CHAPTER 51

DRUGS USED IN THE CHEMOTHERAPY OF AMEBIASIS

EMETINE, CHINIOFON, VIOFORM AND CARBARSONE

Amebiasis is a disease resulting from invasion of tissues of man by a pathogenic ameba, *Endameba histolytica.* The invasion nearly always occurs through the mucosa of the large bowel. Symptoms vary from slight digestive upsets to severe dysentery and constitutional manifestations. Abscesses of the liver and also of the lung and brain may occur. *Amebic dysentery* is a symptom-complex in which bloody mucoid diarrhea is the presenting feature. It is only one of the results of amebiasis. The majority of amebic infections are not accompanied by dysentery, but only by mild symptoms usually not recognized as due to the pathogenic ameba.

Amebiasis is worldwide in distribution. It can no longer be considered a tropical disease. Indeed, in some districts in the temperate zone where sanitary conditions are poor, the incidence may be almost as high as in warm countries. In the United States, where the infection is widespread, it has been conservatively estimated that from five to 10 per cent of the population harbor the organism. As a result of the Chicago epidemic of 1933–1934, the incidence is now probably greater. A summary given by Craig (1934) of various reliable surveys made in representative groups and areas in the United States shows that 5720 of 49,336 persons examined harbored the organism, an incidence of 11.6 per cent. Since only a relatively small percentage of infected patients suffers from the disease, the number of asymptomatic carriers is exceedingly large.

The causative organism, *Endameba histolytica,* was first discovered in 1875 by Lösch while examining a stool of a patient with dysentery in St. Petersburg, Russia. Sir William Osler was the first one in the United States to demonstrate the amebae in a case of dysentery and liver abscess. Endameba histolytica is a unicellular parasite which needs no intermediate host for the completion of its life cycle. It is actively motile, shows pseudopodic activity, has a clear refractile ectoplasm, often contains ingested red blood cells, and is usually 20 to 30μ in diameter. The parasite enters a cyst stage in which it is five to 20μ in size and contains not more than four nuclei. It must be differentiated from nonpathogenic amebae found in the human colon, *Endameba coli* and *Endameba nana. Endameba histolytica* is transmitted from man to man by food or drink contaminated with cysts of the parasites. Only the cysts are infective, because the motile forms (trophozoites) are killed by the gastric juice. The person with acute amebic dysentery is not so much concerned in the transmission of the disease because cysts rarely occur in his feces; the real menace is the healthy carrier or the convalescent patient who has cysts in his stools.

In the large intestine, the cysts give rise to young amebae which become motile and are known as trophozoites. The latter multiply by simple fission, attack the mucosa of the intestine, dissolving and penetrating it by virtue of their motility and a cytolytic substance they excrete, and thus produce the ulcerations characteristic of amebic dysentery. Only the motile forms invade tissues where they may lead to abscess formation. The liver is the chief site of amebic abscess. Cysts are not found in the tissue of the intestine, or in abscesses of the liver, brain or lungs. Encystment apparently occurs only in the lumen of the bowel and when conditions for vegetative existence become unfavorable. The motile amebae and cyst forms differ in their susceptibility to amebicidal agents.

Classification of Amebicides. Amebicidal drugs may be classified as follows:

1. *The emetine group.*
   Ipecac
   Emetine
   Emetine bismuth iodide
2. *The oxyquinoline derivatives.*
   Chiniofon
   Vioform
3. *The organic pentavalent arsenicals.*
   Carbarsone
   Treparsol
   Acetarsone
4. *Miscellaneous drugs and adjuvants.*

IPECAC

This drug was introduced into Europe in 1658 from Brazil where the natives used a decoction of the root in the treatment of diarrheas. Its more recent use dates from the 1840's when ipecac was employed in India as an efficient symptomatic treatment for certain types of dysentery. The source of the drug is the dried roots or rhizome of *Psychotria* (*Cephaëlis*) *ipecacuanha* or *acuminata,* plants native to Brazil and Central America, but also cultivated in India, the Straits Settlements and the Federated Malay States.

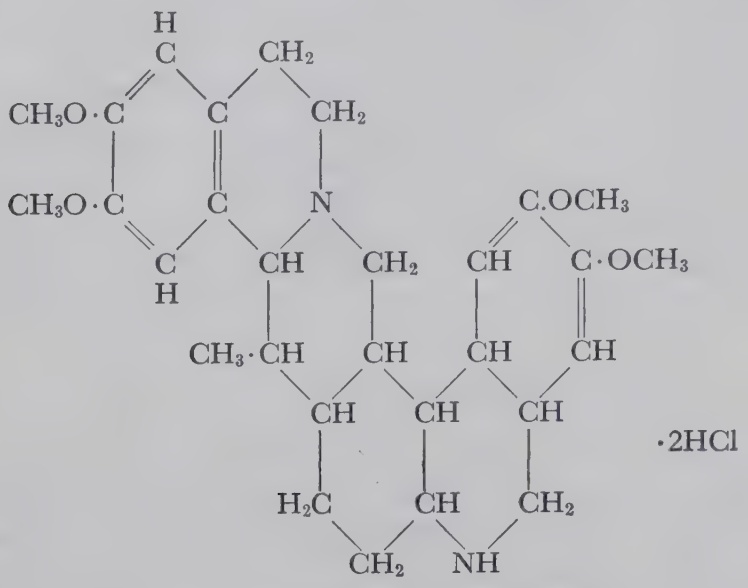
Active Principles. The efficiency of ipecac depends upon its content of alkaloids, the principle ones being *emetine* and *cephaeline*. Both of these are amebicidal but emetine is the more active. Cephaeline is more toxic than emetine except for the heart, and causes more nausea and vomiting. Emetine constitutes more than one-half the total alkaloid content of ipecac.

Status and Use. *Ipecac* is official in the U.S.P and B.P. It has all the actions of emetine as well as the added effect of cephaeline, and is available in powder form or as the fluidextract. It is so difficult to administer, however, due to the severe gastro-intestinal irritation which it causes, that it is rarely used. The drug is not employed in amebiasis unless the patient has proved refractory to more modern treatment. If prescribed, ipecac is given as the dried powder in salol-coated pills as a means of lessening the severe irritation and vomiting. The dose is 10 to 15 pills of 0.3 gram each, given at night before retiring. Ipecac should not be given in divided doses. The full course consists of 100 pills and the patient should be at absolute rest in bed during the treatment. Tincture of opium may be needed to control nausea and vomiting which nevertheless may be so severe as to necessitate cessation of the drug. The other uses of ipecac are discussed elsewhere (*see* Index).

EMETINE

Emetine was first described in 1817 by Pelletier, the discoverer of quinine in cinchona bark. What Pelletier was actually dealing with, however, was a mixture of the alkaloids of ipecac, that is, emetine, cephaeline, and psychotrine. Bardsley, in 1829, was apparently the first to use emetine in diarrheas and dysenteries. Vedder in 1912 demonstrated that emetine killed amebae *in vitro* in a dilution of 1:100,000, and that ipecac deprived of emetine was a poor amebicide. Vedder suggested that emetine might prove valuable for the therapy of amebiasis. Rogers, in the same year, acted on this suggestion and obtained good effects from the drug in amebic dysentery and hepatitis.

Chemistry and Preparations. *Emetine Hydrochloride,* U.S.P., B.P., is the official salt of the alkaloid. The structural formula is as follows:



Emetine Hydrochloride

Emetine hydrochloride is a white or very slightly yellowish crystalline powder, freely soluble in water and in alcohol. It is very irritating and should not come in contact with mucous membranes, especially the conjunctiva. The drug is available in hypodermic tablets, and in solution in ampules for parenteral use (15, 30 and 60 mgm).

Absorption and Fate. Emetine is absorbed from parenteral sites of administration and is excreted or detoxified slowly. Although it appears in the urine 20 to 40 minutes after injection, it can still be found there 40 to 60 days after treatment has been discontinued. Therefore, a cumulative toxic action is an ever present danger.

Mechanism of Amebicidal Action. Emetine has a direct lethal action on *Endameba histolytica.* The drug is much more effective against the motile forms than against the cysts. Concentrations of emetine necessary to kill cystic forms cannot safely be obtained in man. It is of some interest to note that much of the earlier *in vitro* work indicated that the parasite was not killed unless concentrations of emetine of 1:10,000 to 1:50,000 were used. Later work, however, which employed more suitable media for culturing the parasites, clearly demonstrates that dilutions of emetine of 1:1,000,000 to 1:5,000,000 are quite effectively amebicidal. Such concentrations are readily reached in the body after therapeutic doses.

Toxicity. Emetine frequently causes toxic symptoms, especially noted when its action is cumulative from too high dosage or from prolonged therapeutic use. Emetine is a "general protoplasmic poison," and causes hyperemia, cloudy swelling and cellular degeneration in the liver, heart, kidneys, and skeletal muscles. The myotoxic action is particularly evident on heart muscle (Rinehart and Anderson, 1931). Emetine may produce cardiac arrhythmias and can cause a severe acute degenerative myocarditis which may result in sudden cardiac failure or death. Myositis, muscular weakness, tremors and pain, especially in the arms and legs, are also prominent manifestations of emetine poisoning. Edema may also occur, perhaps secondary to the muscle injury and inactivity, perhaps due in part to the cardiac weakness. It has long been thought that emetine caused a peripheral neuritis and that the muscular pain, weakness, and wrist and foot drop were due to peripheral nerve involvement. Young and Tudhope (1926), however, were unable to find pathological evidence of neuritis and attribute the symptoms entirely to the toxic muscular action of emetine. In severe cases, purpuric skin rashes and hemoptysis may occur.

Nausea, vomiting and vertigo may occur after emetine. Severe diarrhea is not uncommon and the stools may be bloody. This results in great prostration and depression. The diarrhea is due directly to the alkaloid and must not be mistaken for a recrudescence of the amebic dysentery, which is often greatly benefited by emetine.

Clinical Efficacy and Use. The main use of emetine in medicine is for the treatment of amebiasis. Despite the apparent highly amebicidal property of emetine *in vitro,* it is generally agreed that the alkaloid alone does not result in the *cure* of amebic infection in more than 10 to 15 per cent of patients. While symptoms readily disappear during the first course of emetine in acute cases of intestinal amebiasis, more than 50 per cent of patients later show cysts in their feces. These patients therefore become carriers, with all the attendant dangers to themselves and the general public. Treatment of asymptomatic carriers with emetine is notoriously unsuccessful. Although both motile amebae and cysts disappear during emetine medication in acute dysentery, cysts reappear in the stools at varying periods after therapy has been discontinued. Further emetine therapy usually does not eliminate these cysts.

The only valid use of emetine in intestinal amebiasis is for severe cases of amebic diarrhea and acute amebic dysentery, or in acute exacerbations of chronic amebic dysentery. The drug should be given only long enough to control the diarrheal or dysenteric symptoms. It should never be administered in doses larger than 60 mgm per day, or for periods longer than 10 to 12 days. It has no place in the treatment of patients with mild symptoms or carriers. Emetine is more efficient in curing symptoms of amebiasis than in curing the disease itself. The alkaloid is of particular value in surgical amebic lesions, such as abscesses, and in amebic hepatitis.

Contraindications. Emetine should not be used if organic disease of the heart or kidneys is present. It is also contraindicated in children unless there is severe dysentery which has failed to respond to other measures. Emetine is best not used during pregnancy.

Dosage and Administration. The preferred route of emetine administration is the subcutaneous (Craig, 1934), although some recommend intragluteal injection. The intravenous use of emetine is contraindicated.

The dose of emetine hydrochloride for adults should not be more than 60 mgm per day. This can be given in a single injection or in 30 mgm portions morning and evening. A course of emetine therapy should not continue for more than 10 days, the total dose not exceeding 0.6 gram. For children over eight years of age, not more than 20 mgm should be given daily; for children under eight, the daily dose should not exceed 10 mgm. A safe plan to follow is to administer emetine on the basis of body weight, employing not more than 1.0 mgm of alkaloid per kg per day, or 10 mgm per kg per course (Anderson and Leake, 1930). Usually, emetine causes rapid disappearance of symptoms within three or four days and is then replaced by carbarsone, chiniofon or vioform. A course of emetine may not be repeated until a rest period of at least six weeks has intervened.

The patient must be observed closely during emetine therapy for early evidences of untoward symptoms. The blood pressure should be measured twice daily. The patient must remain in bed during and for several days after the period of drug administration. Emetine is discontinued immediately if signs of toxic effects appear.

EMETINE BISMUTH IODIDE

DuMez (1915) first reported on the use of emetine bismuth iodide in amebiasis in the Philippine Islands. The compound contains 25 to 28 per cent of anhydrous emetine, and 18 to 21 per cent bismuth, and is prepared by precipitation of a solution of emetine hydrochloride with a solution of potassium bismuth iodide. The bismuth content does not result in any demulcent action because the dose is too small.

The advantage of the compound is that it affords a means of oral medication with emetine, the hypodermic injection of which is often painful and may result in tissue induration and slough.

Toxicity. The toxicity of emetine bismuth iodide is the same as that of emetine. It is impossible to escape some nausea and diarrhea, and if these are severe or if much vomiting occurs the drug should be stopped. The heart rate and rhythm and the blood pressure should be followed closely, and medication halted if signs of cardiac embarrassment appear. The treatment often leaves the patient weak and mentally depressed.

Dose and Administration. Emetine and Bismuth Iodide, B.P., is a reddish-orange, odorless, bitter powder, insoluble in water and alcohol. The dose of emetine bismuth iodide is 0.2 gram, given in hard gelatin capsules after the evening meal once daily for twelve consecutive days. The patient must be kept in bed during and for a few days after the treatment. Nausea and vomiting almost invariably occur the first night or two, and diarrhea appears after four to five days. The treatment may be repeated after a rest period of four weeks if amebae are still present in the stool.

Clinical Status and Use. Although the action of emetine bismuth iodide is essentially that of emetine itself, the drug is a more powerful amebicide. The iodine content probably accounts for the greater potency, or perhaps it is the use of the oral route which may result in some unabsorbed drug reaching the large bowel.

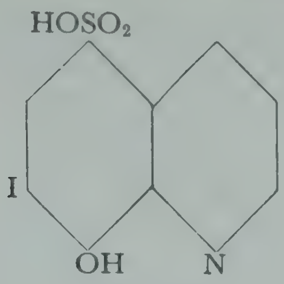
Emetine bismuth iodide is not as effective clinically in amebiasis as carbarsone, chiniofon or vioform. Furthermore, the unpleasant symptoms which constantly attend its administration make its use as routine therapy difficult and undesirable. The drug should never be employed in the treatment of carriers, either with or without symptoms, or in patients who are ambulatory. Its administration requires confinement to bed which entails both time and financial loss, and toxic complications are not rare.

Other compounds of emetine which have been used in amebiasis are *emetine periodide* and *auremetine.* Neither can be recommended.

CHINIOFON

Chiniofon was introduced by Mühlens and Menck in 1921 under the name of *yatren.* It was first marketed as "Yatren 105" which also contained powdered opium. Chiniofon is official in the U.S.P. *Anayodin* is a proprietary preparation of chiniofon.

Chemistry. Chiniofon is an iodoxyquinoline derivative—7-iodo-8-oxyquinoline-5-sulfonic acid. *Chiniofon Powder,* U.S.P., consists of a mixture of chiniofon, its sodium salt and sodium bicarbonate. It contains about 27.5 per cent iodine. Chiniofon powder dissolves in about 25 parts of water with effervescence, and forms the sodium salt as it goes into solution. The powder is canary yellow in color, having a bitter taste and sweet after-taste. It is also official in the B.P. The structural formula of chiniofon is as follows:



Chiniofon

Amebicidal Action. Chiniofon has a direct amebicidal action which is due to its iodine content. *In vitro* tests do not indicate the true *in vivo* potency of chiniofon because, although the drug kills amebae, the dilution in which this occurs is not striking. The chemical is clinically effective against both motile and cyst forms. Chiniofon is somewhat less rapid than emetine in its action against motile forms. It is ineffective in amebic abscess and hepatitis, and apparently acts only on organisms in the intestinal tract.

Preparations and Doses. Chiniofon is marketed in bulk as a dry powder in amber bottles, and also as 0.25 gram enteric-coated tablets.

The dose of chiniofon is 0.75 to 1.0 gram, given as tablets three times a day with meals. A course of chiniofon consists of medication for eight to 12 days. It is best to start with two or three 0.25 gram tablets per dose for the first three or four days of medication in order to avoid the diarrhea which may accompany larger initial doses. The dose for children is regulated according to age. The drug is also given rectally as a retention enema, six grams being dissolved in 300 cc of warm water for this purpose. The enema is retained as long as possible and may be repeated each night for a week or 10 days. The oral dose of chiniofon should not exceed 0.5 gram three times daily while nightly enemata are employed.

Toxicology. Chiniofon is non-toxic in therapeutic doses. Many thousands of patients have been treated with chiniofon without reports of serious toxic symptoms or injury to health even after repeated courses. Given intravenously, the drug has caused death, but there is no need or excuse for using it by this route.

The only untoward effect noted with chiniofon is a more or less profuse diarrhea which many patients develop after full doses. This lasts only two or three days, as a rule, and is usually not excessive. Infrequently, the diarrhea is severe enough to require discontinuance of therapy. Intolerance and mild symptoms of iodism are rare. Experimentally, chiniofon in high doses may occasionally produce liver damage.

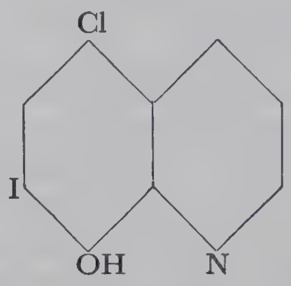
Contraindications. Chiniofon should not be used in the presence of iodine intolerance, and must be given with caution to patients with thyroid disease. Liver damage is also a contraindication. In those individuals in whom a persistent and severe diarrhea occurs from the drug, chiniofon should not be given.

Clinical Status and Use. Chiniofon is effective in all forms of acute and chronic intestinal amebiasis. Craig (1934) and O'Connor and Hulse (1935) believe that this chemical is the safest and most efficient amebicide. Although chiniofon fails in a small percentage of cases, the majority respond well when the drug is properly given. It has the advantage of being less toxic than any known arsenical amebicide and can therefore be used in mass treatment of ambulatory patients, especially carriers. Some physicians recommend rest in bed during treatment with chiniofon but this is not necessary unless the severity of the disease itself demands it. If necessary, one may use chiniofon in courses alternating with carbarsone.

VIOFORM

Vioform was originally proposed as a substitute for iodoform and is used as a dusting powder for skin wounds, ulcers and burns. Its possible employment in amebiasis was suggested by the excellent results with chiniofon. The first experimental report was that of Anderson and Koch (1931) on the effect of vioform in amebiasis in monkeys. The first clinical report was that of David, Johnstone, Reed and Leake (1933).

Chemistry. Vioform is iodochlorhydroxyquinoline. Its structural formula is as follows:



Vioform

Vioform is a grayish-yellow powder with faint odor, and is almost insoluble in water. Its iodine content is about 50 per cent greater than that of chiniofon powder, being not less than 37.5 per cent or more than 41.5 per cent. The drug is a local irritant and cannot be used rectally as can chiniofon.

Amebicidal Action. Vioform, like chiniofon, is directly amebicidal due to its iodine content.

Preparations and Doses. *Vioform* (*N.N.R.*) is given in the form of 0.25 gram enteric-coated tablets or gelatin capsules. The dose is 0.25 gram three or four times a day for ten days, which constitutes a "course." A rest period of at least a week to ten days should intervene before the course is repeated. Vioform may be given in courses alternated with carbarsone.

Toxicity. Toxic reactions are almost as negligible with vioform as with chiniofon. Mild iodism may occur due to the higher iodine content. Some increase in gastro-intestinal symptoms may be noted and approximately one in twenty patients has severe gastric distress. The *contraindications* for vioform are the same as for chiniofon.

Clinical Status and Use. Vioform has the same uses as chiniofon but it cannot be given rectally. Like chiniofon, it is effective only in intestinal amebiasis, whether acute or chronic, but more so in the latter, and acts both on the motile and cystic forms of amebae. Vioform is useful for ambulatory and mass treatment, is inexpensive and does not require rest in bed or special routine. Reed (1935) ranks it as the superior oxyquinoline amebicide and second only to carbarsone as an anti-amebic drug. Craig (1934) prefers chiniofon because of the excellent results and more extensive clinical experience that have been obtained with it.

Vioform is also effective in the treatment of *Trichomonas vaginalis vaginitis*, for which purpose it may be used locally in an ointment form or insufflated as a powder (one part in nine parts of magnesium trisilicate). Best results are apparently obtained by the oral administration of vioform combined with the local use of the powder (Zener, 1939).

CARBARSONE

Carbarsone was first prepared by Ehrlich. It was introduced in the therapy of amebiasis by Anderson and Reed (1931), and was extensively studied by Reed and collaborators (1932). Carbarsone is accepted by N.N.R.

Chemistry. Carbarsone is an organic pentavalent arsenical, p-carbamidobenzene arsonic acid. It is closely related to tryparsamide, especially in having an amino group in the para position to the arsenic. It contains 28.5 per cent arsenic. The structural formula of carbarsone and its relation to acetarsone and treparsol are shown on page 736 in connection with the general pharmacology of arsenic.

Amebicidal Action. Carbarsone is directly amebicidal by virtue of its arsenic content. It is more effective than acetarsone and has a therapeutic index eight times higher. Like chiniofon, the action of carbarsone on motile forms, although effective, is not as rapid as that of emetine. Carbarsone does not act on amebae in abscesses of the liver and other organs. The drug is active against cysts.

Preparation, Dose and Administration. Carbarsone is a stable, almost odorless white powder. It is insoluble in water but soluble in dilute alkali. The drug is marketed in tablets containing 0.05 and 0.25 gram, in gelatin capsules containing 0.25 gram, in vials containing two grams, and in rectal suppositories containing 0.12 gram. All are N.N.R. preparations.

The adult dose of carbarsone is 0.25 gram taken *orally* twice daily for ten days. This constitutes a "course" which may be repeated several times if necessary, but only after rest periods of ten days. The arsenical may be alternated with courses of chiniofon or vioform. Doses for children are calculated according to weight. Carbarsone can also be given *rectally* as a retention enema and is used in this manner for acute dysentery with motile amebae in the stool. A cleansing enema and a sedative are first given, and then 200 cc of a warm solution of one per cent carbarsone in two per cent sodium bicarbonate are administered. The enema is repeated every other night until five enemata have been retained over night. Carbarsone by mouth is omitted while the rectal route is being used. Rest in bed is not required during carbarsone medication.

Absorption and Excretion. Carbarsone is absorbed readily after oral administration and is excreted rather slowly in the urine. Rest periods between courses are therefore imperative to prevent cumulative toxic effects.

Toxicology. Carbarsone appears to be one of the most innocuous of the organic arsenicals. Considering the wide use of the drug, few cases of serious poisoning have been reported. Despite the para position of the amino group, serious *optic damage* is almost unknown (page 955). Skin rashes of varying severity, but usually mild, and localized edemas are occasionally observed. Severe exfoliative dermatitis, however, is practically unknown after carbarsone. Death from carbarsone is extremely rare (Epstein, 1936). Exacerbation of diarrhea, mild nausea and vomiting, and vague abdominal pains may sometimes occur.

Clinical Status and Use. Reed (1935) is of the opinion that carbarsone is the best of all amebicidal drugs. Craig (1934) places it second to chiniofon. The chemical has several distinct advantages. It can be given orally, and also rectally if necessary. It is the most potent and least toxic arsenical amebicide, is as effective as any other single agent, and rarely causes serious toxic effects. Carbarsone requires no special adjuvants, bed rest or diet, and can therefore be used in carriers and mild ambulatory cases. It is useful and effective in both acute and chronic cases, and against both motile and cystic forms of the parasite.

Carbarsone has also been found effective for the local treatment of *Trichomonas vaginalis vaginitis.*

Disadvantages and Contraindications. Carbarsone is not effective against amebic infections other than those of the enteric tract. Mass treatment cannot be undertaken with the drug unless strict medical supervision is possible. The patient's vision and skin especially must be carefully observed. Carbarsone is contraindicated if renal or hepatic disease is present. Reed (1934), who has had considerable experience with carbarsone, recommends that a liver function test be performed before using the arsenical.

TREPARSOL

Treparsol is an organic pentavalent arsenical which differs from acetarsone in that it has a formyl group in place of the acetyl. Its structural formula is given on page 736.

Status. Treparsol apparently is an effective amebicide and has been used in combination with emetine hydrochloride (Brown, 1928, 1935). It is less toxic than acetarsone, due especially to its more rapid elimination, but is more toxic than carbarsone, which has therefore largely replaced treparsol as the arsenical of choice in amebiasis. Treparsol is given in courses lasting four days, the dose being a single 0.25 gram tablet three times daily with meals. Three courses are given with intervening rest periods of 10 days each. The drug is not official and is not included in N.N.R.

ACETARSONE

Acetarsone is also known as *stovarsol, spirocide* and *"Fourneau 190."* It was introduced by the French for the oral treatment of syphilis. The *oral use* of acetarsone in *syphilis of adults* or in *congenital syphilis in children* is based on insufficient clinical and experimental evidence and cannot be recommended. The drug was first used in amebic dysentery by Marchoux (1924). It is official in the B.P. and is included in N.N.R.

Chemistry and Amebicidal Action. Acetarsone is a synthetic pentavalent organic arsenical, 3-acetylamino 4-hydroxyphenylarsonic acid, the structural formula of which is given on page 736. The drug contains approximately 27 per cent of arsenic and is a white crystalline powder, insoluble in cold water and alcohol. Its amebicidal action is directly due to its arsenic content. The poor antisyphilitic potency of acetarsone has been attributed to the acetylation of the amino group, any change in which decreases the antispirochetal efficacy of meta-amino parahydroxyphenylarsonic acid.

Dosage. The drug is supplied in tablets containing 0.5, 0.25 and 0.1 gram. The recommended dose is 0.25 gram three times daily for seven days, followed by a rest period of a week and then another seven days of medication.

Clinical Uses and Status. Acetarsone therapy of *amebiasis* does not interfere with the daily routine of the patient and can be employed in ambulatory cases or in carriers. It should not be used in acute amebic dysentery, or in cases that cannot be closely observed at frequent intervals by the physician. Its limitations are essentially those of carbarsone. The likelihood of arsenical poisoning is much greater with acetarsone than with carbarsone and the latter drug is therefore to be preferred in amebic infections. Acetarsone has only one-eighth the therapeutic index of carbarsone, and arsenical poisoning occurs in approximately one of six patients. Doses that have reasonable effectiveness are too toxic.

Acetarsone has been employed locally in the vagina for the treatment of *Trichomonas vaginalis vaginitis*, in the form of a powder containing 12.5 per cent acetarsone in a mixture of equal parts of kaolin and sodium bicarbonate. The single dose of powder is four grams containing 0.5 gram of the arsenical, administered by insufflation. Acetarsone has been used as a paste in the local treatment of *Vincent's angina*. The drug has also been recommended for the therapy of *Boeck's sarcoid.*

MISCELLANEOUS AMEBICIDAL AGENTS

A large number of miscellaneous amebicidal agents exist but the vast majority of these are not serviceable in the modern therapy of amebiasis. Among these are kurchi bark (employed in India), kurchi bismuth iodide, chaparro amargosa (a Mexican plant), dihydranol (heptylresorcinol), mercury and silver salts, arsphenamines, quinine, etc. In addition, numerous medicated enemata have been instilled into the colon. Even kerosene was employed at one time. None of these agents can compare in efficacy with carbarsone, chiniofon or vioform.

Bismuth. Bismuth is useful as a non-specific adjuvant in the therapy of intestinal amebiasis. It acts as an antidiarrheal and demulcent, assists in decreasing inflammation, bacterial growth and putrefaction, and alters the environment of the amebae so that degenerative changes in the parasites may be hastened. Bismuth subcarbonate may be employed in combination with specific amebicidal drugs. The dose is 12 grams (a heaped teaspoonful), given well stirred in a glass of milk or water every four hours day and night in cases of severe dysentery. The dose is decreased as improvement occurs.

PRINCIPLES OF THERAPY OF AMEBIASIS

The modern therapy of amebiasis includes not only the treatment of patients with acute amebic dysentery but also those persons who have intestinal amebiasis without acute symptoms. The intestine can harbor the parasite and yet the individual may remain symptom-free, but the carrier remains a potential source of infection to himself and others and is an extremely serious public health problem, especially if he handles food. Amebic abscesses of the liver, brain and lung may develop in carriers who have had little or no previous symptoms of intestinal amebiasis.

The physician has at his disposal four potent amebicidal agents—emetine, carbarsone, chiniofon, and vioform. These differ in their usefulness dependent upon the character of the amebic infection. Emetine, formerly viewed as a specific cure for amebic dysentery, is now known to be the least valuable agent for *curing* the disease but the most potent one for rapidly controlling the symptoms of severe intestinal infections. Because it does not kill cyst forms, emetine will not cure intestinal amebiasis and is valueless for carriers. In sharp contrast to its restricted usefulness in acute amebic dysentery, emetine is the only amebicide of value in the treatment of amebic hepatitis and amebic abscesses of the liver and other organs.

Carbarsone, chiniofon and vioform have the same field of usefulness in the therapy of intestinal amebiasis, but the three drugs are valueless for amebic infections of the liver, brain and lung. Carbarsone in particular is contraindicated in cases with liver involvement. Both cystic and motile forms of amebae in the intestinal tract are killed by these chemicals, and when properly employed approximately 90 per cent of patients can be cured by one or two courses of medication.

The decision as to whether amebic infection of the intestinal tract has been cured depends on laboratory and not medical examinations. Disappearance of symptoms does not mean cure of amebiasis. Evidence of cure is acceptable if it consists of negative stool examinations at weekly intervals for four weeks after completion of treatment, and at monthly intervals thereafter for five months. Repeated courses of medication are sometimes required to effect a cure. Treatment should be resumed whenever the stool again becomes positive for amebae.

Only the general principles of therapy of amebiasis with specific chemotherapeutic agents can be reviewed here. The details of treatment as well as the many adjuvant and dietary measures employed must be sought elsewhere (*see* Craig, 1934; Beckman, 1938). The doses, indications, contraindications and toxicity of the anti-amebic drugs have already been given.

Treatment of Carriers. Emetine is useless in the treatment of carriers. Carbarsone, chiniofon or vioform should be employed. These agents are effective against amebic cysts and do not entail rest in bed, special routine, interruption of work or discomfort. Furthermore they may be taken orally. If one course of medication does not establish a cure, carbarsone and chiniofon or vioform may be alternated with each other in courses. Both the asymptomatic carrier and the carrier with mild intestinal symptoms may be treated in this manner. The patient must be more closely observed when receiving carbarsone than when an oxyquinoline drug is given.

Amebic Diarrhea or Enteritis. Mild cases may remain ambulatory during therapy and are managed in a manner similar to that for carriers. More severe cases require rest in bed and are given a course of carbarsone, chiniofon or vioform. If symptoms are quite severe, injections of emetine in doses of 30 mgm daily may be required for several days. Otherwise emetine is not employed. Several courses of medication may be needed, in which circumstance carbarsone may be alternated with chiniofon or vioform.

Acute Amebic Dysentery. The patient should be kept in bed. Emetine has no equal for controlling acute symptoms of severe amebic dysentery. It is injected for a period not longer than 10 days and the total daily dose should not exceed 60 mgm. As a rule, symptoms subside within a few days and the stools become formed. Emetine is discontinued as soon as the acute symptoms are under control, and carbarsone, chiniofon or vioform is substituted. It is quite possible in most cases to treat acute severe amebic dysentery without resort to emetine, but improvement is not so dramatic. The toxic effects of emetine, however, are avoided. Enemata of carbarsone or chiniofon may then be necessary in addition to oral therapy. Milder forms of acute amebic dysentery do not necessitate emetine therapy.

Combined therapy with carbarsone and chiniofon may often be employed to advantage in patients with acute amebic dysentery, as well as in those with latent intestinal amebiasis with or without symptoms. As pointed out by Mateer and coworkers (1940), combined therapy of this type may reduce the percentage of failures from 10 per cent to as low as three per cent. Thus, in a series of 104 patients with various forms of acute and chronic intestinal amebiasis, these investigators obtained successful results in 97 per cent, repeated examinations of the stools revealing persistent absence of amebae for the period of observation (six months to three and one-half years). The regimen employed was as follows: carbarsone was given orally for 10 days in the dose of 0.25 gram twice daily—after breakfast and after supper; chiniofon was administered as a retention enema (250 cc of a 2.5 per cent solution) every other morning for 10 days. No drug reactions were encountered.

Symptoms and signs suggestive of acute appendicitis occurring in a patient during the course of active intestinal amebiasis call for treatment with emetine followed by chiniofon, carbarsone or vioform. Craig (1934) considers an operation on such a patient to be unwise, if indeed not contraindicated. He points out that surgical intervention may be serious or fatal due to the fact that the appendicitis is nearly always a manifestation of amebic invasion of the appendix rather than an intercurrent non-specific infection, and that there is usually coincident involvement of the cecum. Relief is obtained promptly as a rule by the use of amebicidal drugs.

Chronic Amebic Dysentery. Patients with acute exacerbations of chronic long-standing amebic dysentery should be put to bed and managed as outlined for the acute initial attack. If the symptoms are mild or if the disease is in a relatively quiescent stage, the patient may remain ambulatory and is treated as described for carriers or those with mild enteritis.

Treatment with specific amebicidal agents should not be instituted unless it is established by proper stool examinations that the symptoms are due to the pathogenic amebae. As Craig (1934) has emphasized, patients who have had amebic dysentery for several years and who eventually have been cured may continue to experience attacks of diarrhea due to altered bowel function and extensive scarring resulting from the previous intestinal ulceration. Diarrhea may be noted especially when the fluid intake is large or after dietary indiscretions. The history may often be elicited from such individuals of having received repeated courses of anti-amebic therapy, usually with emetine. On the basis of the diarrhea and the history of previous amebic infection, the diagnosis of recrudescence of infection is made. Only examination of the stools for the parasites can establish the diagnosis of intestinal amebiasis. Repeated courses of emetine therapy are dangerous, and the patient should be informed, after repeated stool examinations have failed to reveal pathogenic amebae, that he is no longer infected and that episodes of diarrhea may be experienced from time to time.

Amebic Abscesses. Amebic abscesses of the liver and other organs are always secondary to intestinal infestation with *Endameba histolytica.* A history of symptoms of intestinal amebiasis cannot always be elicited and abscesses may occur in asymptomatic carriers. Only motile forms of amebae are found in abscesses.

Emetine, despite its limitations for the therapy of intestinal amebiasis, is the agent of choice for treating amebic hepatitis or abscess. Early recognition of amebic hepatitis and treatment with emetine prevent abscess formation. Surgery can often be avoided if a liver abscess is treated with emetine in its early stages. Emetine should not be injected for more than 10 to 12 days, and the total daily dose should not exceed 60 mgm. Usually symptoms and signs are relieved within a week, and the fever and elevated white blood cell count fall sharply toward normal. If emetine does not improve amebic hepatitis within a week, suppuration has probably occurred.

The factors concerned in the choice between medical and surgical measures in the treatment of amebic abscesses cannot be given in detail here. Some authorities claim that intensive emetine therapy may completely resolve abscesses of the liver, at times even when these are fluctuating or actually bulging. If striking improvement is not noted after a full course of emetine, surgical intervention is usually indicated. Mixed infections with bacteria or signs of perforation ordinarily call for surgery. Puncture or aspiration of an abscess should not be undertaken unless emetine has been injected for five or six days. A 1:2500 solution of emetine hydrochloride may be employed to irrigate an abscess cavity. Amebic abscess of the lung or brain may also be treated with emetine. Prompt surgery is usually indicated when amebic brain abscesses are diagnosed.

In summary, it may be said that emetine is almost a specific for amebic hepatitis, is often capable in itself of resolving amebic abscesses, especially of the liver, and renders aspiration or surgical measures less hazardous and more effective. Once the patient has been cured of the amebic abscess, attention should be given to eradicating the intestinal focus of infestation, in order to prevent reinfection of the liver. Chiniofon, carbarsone or vioform is the agent of choice for this purpose.

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CHAPTER 52

DRUGS USED IN THE CHEMOTHERAPY OF LEPROSY

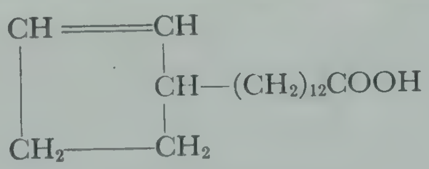
CHAULMOOGRA AND HYDNOCARPUS OILS

Chaulmoogra oil is the most effective agent available for the treatment of leprosy.

Historical. The use of chaulmoogra oil in the treatment of leprosy dates back many centuries. According to ancient Burmese legends, Rama, King of Benares, being a leper, retired to the jungle and subsisted on herbs and fruits. Among others he consumed the fruit of the *kalow* tree which is the Burmese name for *Taraktogenos kurtzii,* one of the present official sources of chaulmoogra oil. The king recovered from his affliction and subsequently married Princess Piya who was also a leper and whom Rama had met in the jungle and cured. In the 14th century in China, Chu Tan-Chi wrote concerning the use of chaulmoogra oil in the treatment of leprosy but disapproved of the drug because of its unpleasant after-effects. The oil was introduced into Western medicine in the middle of the 19th century, but it was not until after 1900 that intensive investigations were undertaken on the chemotherapy of leprosy. Until that time confusion had existed as to the true source of chaulmoogra oil and little was known of its chemical composition.

Source and Chemistry. Chaulmoogra oil is obtained from the seeds of certain trees of the order *Flacourtaceae,* most of which belong to the genus *Hydnocarpus.* The official U.S.P. sources of the drug are *Taraktogenos kurtzii, Hydnocarpus wightiana* and *Hydnocarpus anthelmintica.* The species are indigenous to Siam, India, Burma and Indo-China. Only the oil from the first-named species should properly be called chaulmoogra oil, the product from the other sources being more correctly designated as hydnocarpus oil. The oils, however, are almost identical in their chemical constitution.

The chief active ingredients of chaulmoogra and hydnocarpus oils are two unsaturated fatty acids which have been designated as *chaulmoogric acid* and *hydnocarpic acid.* Both acids are present in each of the oils. The compounds are unique among fatty acids in that they contain a closed ring of five carbon atoms and are optically active, the naturally occurring acids being dextrorotatory. The structure of chaulmoogric acid is presented below. Hydnocarpic acid differs in having two less CH_2 groups.



Chaulmoogric Acid

The aforementioned acids are present in the natural oil as glyceryl esters. The glyceryl esters can easily be converted to ethyl esters, or to the free acids and their sodium salts.

Many derivatives of and compounds closely related to chaulmoogric and hydnocarpic acids have been synthesized and tested for their antileprotic activity. A method for their laboratory evaluation has been outlined by Anderson, Emerson and Leake (1934). No compound has yet been found which is equal in activity to those occurring naturally. Neither can a definite statement be made in regard to the relation between chemical structure and degree of activity of antileprotic drugs. The methods of assay and evaluation are so difficult that conclusions have been at variance. Some investigators consider unsaturation essential for activity, claiming that hydrogenation of the oils renders them inert. Others are of the opinion that the five carbon ring is the basis for activity. Finally it has been stated that the physical properties, especially those of solubility and surface tension, are the important features of antileprotic compounds and that a fatty acid can be active even though saturated and lacking a cyclopenteno group.

Pharmacological Actions. The only important pharmacological action of chaulmoogra oil is that which accounts for its effectiveness in the treatment of leprosy. The mechanism of this action has not been elucidated. Some claim that the fatty acids contained in the oil are directly bactericidal *in vivo*. In support of this contention is the observation that cultures alleged to be *Myco. leprae hominis* and also cultures of other acid-fast organisms are inhibited *in vitro* by relatively high dilutions of the compounds. Another theory is that the fatty acids of chaulmoogra oil exert a solvent action on the fat-containing bacillus, thus liberating an endotoxin which stimulates the immunity response. Others claim that the organism is more vulnerable if its waxy coating is affected by the drugs. Still another view is that chaulmoogra oil is not in itself lipolytic but rather enhances the activity of tissue lipases.

Preparations. There are three major types of chaulmoogra preparations, the natural oil, the esterified oil and the sodium salts of the specific fatty acids. Of these, *sodium hydnocarpate* has had extensive clinical trial. *Chaulmoogra Oil,* U.S.P., is the oil expressed from any of the three species of seeds mentioned above. It is a yellow liquid solidifying at 25 C., with a characteristic odor and acrid taste. The B.P. preparation is obtained solely from *Hydnocarpus wightiana* and is called *Hydnocarpus Oil*. It has the same physical properties as the U.S.P. preparation. The oil, when freshly prepared, is relatively non-irritating and is suitable for parenteral administration. It is viscous and is difficult to inject unless warmed to above body temperature. *Ethyl Chaulmoograte,* U.S.P., is esterified chaulmoogra oil. The name is misleading in that in a strict chemical sense it would refer to the ethyl ester of chaulmoogric acid. The preparation is much more expensive than chaulmoogra oil. It consists of a pale yellow liquid having a slight fruity odor. The corresponding B.P. preparation obtained from hydnocarpus oil is more correctly named, being called *Ethyl Esters of Hydnocarpus Oil*. Ethyl chaulmoograte possesses the advantages of being somewhat less irritating than the non-esterified oil and being less viscous and more easily injected. Some investigators use iodized preparations of the ethyl esters or the esters combined with four per cent creosote in the belief that irritation is reduced. *Sodium hydnocarpate* is not an official drug in the United States but is widely employed where leprosy is prevalent. The drug occurs in powder form which is stable. It is easy to transport because of its small bulk and is the only preparation suitable for intravenous administration.

Therapeutic Uses. Although chaulmoogra oil has been tried in the treatment of infections due to other acid-fast organisms, its only valid use is in the therapy of leprosy, in which condition it is undoubtedly superior to the host of other agents which have been employed. With the development of the improved methods for the use of this drug, the outlook of the leper has changed from one of a lifetime of segregation to a reasonable expectancy of a complete cure, especially if treatment is started early in the course of the disease.

Technics of Medication. These are so varied that details must be sought in special monographs. In the past, chaulmoogra oil was usually administered by mouth or inunction, but the present tendency is toward parenteral injection. There are two major technics for parenteral administration. In one the drug is injected in a conventional manner, *i.e.,* intramuscularly or intravenously. With the other method, the leproma are directly infiltrated by multiple intradermal injections. With each injection about 0.05 cc of the drug is administered. Depending upon the condition of the patient, a total dose of from 0.5 to 5.0 cc (10 to 100 injections) is administered once or twice weekly. The body is carefully mapped so that the entire afflicted area is infiltrated. The drug should not be injected twice into the same area at an interval of less than one month. By this technic not only do high concentrations of drug reach the leproma but also the general systemic effects are obtained once the oil is absorbed. Either freshly prepared oil or esterified preparations can be employed with this technic.

If intramuscular injections are employed, the dose is gradually built up to a maximum of five cc of the oil or ethyl ester once weekly. Courses of intramuscular injections may be alternated with those of intravenous injections of sodium hydnocarpate. Sodium hydnocarpate is employed as a one or two per cent solution in saline and the dose eventually reaches 10 cc twice weekly.

Toxic Reactions. Toxic reactions are prone to follow the administration of chaulmoogra oil or its derivatives, but these, as a rule, are not very serious. Immediate effects may consist of dizziness, pains in the chest and a choking sensation. Some degree of local irritation at the site of injection is common and unless precautions are taken sodium hydnocarpate may cause thrombosis of veins. Generalized symptoms include headache, malaise, fever, weakness, insomnia, anorexia, abdominal pain and a peculiar generalized sensation of heat. That the drug may irritate the kidneys is evidenced by the appearance of albumin and casts in the urine of a significant number of patients. A rather common reaction to therapy is the so-called "leprous reaction." It consists essentially of an intense flare-up of the symptoms of the disease. Many believe the reaction is anaphylactic in character. It must be treated symptomatically, during which time the dose of chaulmoogra oil is either markedly diminished or temporarily omitted.

ANDERSON, H. H., EMERSON, G. and LEAKE, C. D. A pharmacological evaluation of certain antileprotic drugs. *Internat. J. Leprosy,* 1934, **2,** 39–55.

COLE, H. I. Chemistry of leprosy drugs. *Internat. J. Leprosy,* 1933, **1,** 159–194.

FINDLAY, G. M. Recent advances in chemotherapy. P. Blakiston's Son & Co., Philadelphia, 1930.

MUIR, C. Treatment of leprosy; a review. *Internat. J. Leprosy,* 1933, **1,** 407–458.

CHAPTER 53

DRUGS USED IN THE CHEMOTHERAPY OF SYPHILIS

I. THE PHARMACOLOGY AND CLINICAL TOXICOLOGY OF THE ANTISYPHILITIC ARSENICALS

THE ARSPHENAMINES, MAPHARSEN AND TRYPARSAMIDE

It is planned in the following chapters to discuss the organic arsenicals employed in the treatment of syphilis as well as the other agents used in this disease—bismuth, mercury and iodides—to review the salient features and basic principles of modern syphilotherapy, and finally to indicate the value of these agents in the treatment of other spirochetal and trypanosomal diseases.

ORGANIC ARSENICALS

The organic arsenicals comprise an important and indispensable group of chemotherapeutic agents. The field of chemotherapy received its greatest stimulus from the basic systematic researches of Ehrlich and his collaborators in the first decade of the present century. As a result of their contributions and subsequent advances, the physician has at his command a number of potent therapeutic agents which, when used wisely in conjunction with public health measures, bid fair eventually to eradicate the scourge of syphilis. The antisyphilitic arsenicals include the arsphenamines, arsenoxide and tryparsamide. Their relation to other arsenicals employed medicinally is given in Table 41.

Arsphenamine

Historical. After many years of diligent search for an efficient spirocheticidal and trypanocidal agent which could be employed clinically, Ehrlich and his coworkers finally discovered *arsphenamine* in 1907. It was the 606th product in the series being investigated and hence was popularly called "606." The name under which the German dye works patented the chemical was "salvarsan." This name was suggestive of the hope that Ehrlich held for the drug, namely, that it would prove the salvation of mankind. The term "arsphenamine" did not come into use until the World War of 1914–1918 when the German patents were abrogated in the United States and taken over by the Chemical Foundation. The drug is now official in the U.S.P. Synonyms for it include "diarsenol" and "arsenobenzol."

Arsphenamine came into wide use in syphilotherapy in 1909–1910 and treatment with this drug was based on Ehrlich's concept of "therapia sterilisans magna," that is, therapeutic sterilization of the body after a few large doses of drug. Unfortunately, this was not true for arsphenamine, and it was not appreciated until some years later that many months of continuous treatment are necessary to control syphilis. Considerable harm came from injecting a few doses of arsphenamine and dismissing the patient as cured when the Wassermann reaction became negative or visible lesions healed.

Chemistry. Arsphenamine, an amorphous yellow powder, is 3–3′ diamino 4–4′ dihydroxyarsenobenzene, the formula of which is given in Table 41. This is known as *arsphenamine base*. Because the base is insoluble and unstable, the drug is marketed as the soluble dihydrochloride acid salt which contains 32 per cent of arsenic in the trivalent form. When marketed in nitrogen-filled or vacuum-sealed ampules and stored in a cool place, the drug keeps quite well.

The U.S.P. term "arsphenamine" refers to the dihydrochloride salt. All official preparations must comply with the requirements for purity and toxicity of the National Institute of Health, United States Public Health Service, and must bear labels stating the expiration date beyond which the drug must not be used. This date must not be more than five years from the time of manufacture.

Preparation and Administration. Injection of the acid (dihydrochloride) salt is extremely dangerous and for this reason acid arsphenamine must be treated with alkali to form the disodium salt before it is administered. This requires a special technic and errors in detail may result in serious poisoning or death. The dose, lot number and manufacturer of the preparation used should be recorded for reference in case of accident. The technic of alkalinization is fully described in the N.N.R., texts on syphilotherapy, the public health service venereal disease information reprints,* etc., and can usually be found in the package information accompanying the drug. The salient features are as follows:

After the ampule is inspected for cracks by immersion in alcohol, and for lumping or color change of the drug, it is opened with sterile precautions and sprinkled into sterile distilled water or 0.5 per cent sodium chloride solution contained in a sterile Erlenmeyer flask. For each 0.1 gram of drug, 10 cc of fluid are used, and the drug is allowed to dissolve. Shaking may be necessary to effect solution and does not increase the toxicity of acid arsphenamine.

Alkalinization is then accomplished by one of two methods. The *exact method* requires that 0.85 cc of a normal (four per cent) solution of sodium hydroxide be added for each 0.1 gram of acid arsphenamine. One manufacturer now supplies ampules containing an exact amount of sodium hydroxide solution for the proper alkalinization of arsphenamine. The *approximate method* allows the addition of a solution of alkali drop by drop, regardless of its concentration. A precipitate of the free base is first formed and with the continued administration of alkali this is redissolved as the monosodium salt. Shaking (aeration) is not permissible at this stage. In order to make the disodium salt, an additional quantity of alkali is added which is equal to one-third the amount already used up to the point of complete solution of the monosodium salt. The chemical steps involved in alkalinization are shown in Table 47, and the pH at each stage (Elvove and Clark, 1924) is indicated. Some physicians inject the monosodium salt but reactions are more likely to occur. Others prefer a mixture of monosodium and disodium salts which is less irritant to veins.

After alkalinization is complete, the solution is filtered through sterile gauze (four ply), and an additional amount of water or 0.85 per cent sodium chloride solution is added to make a final volume of 20 cc of solution for each 0.1 gram of drug employed. This solution must then stand protected from air for 30 minutes before being injected. Solutions which have stood longer than three hours should not be employed because toxic oxidation products, especially arsenoxide, may form.

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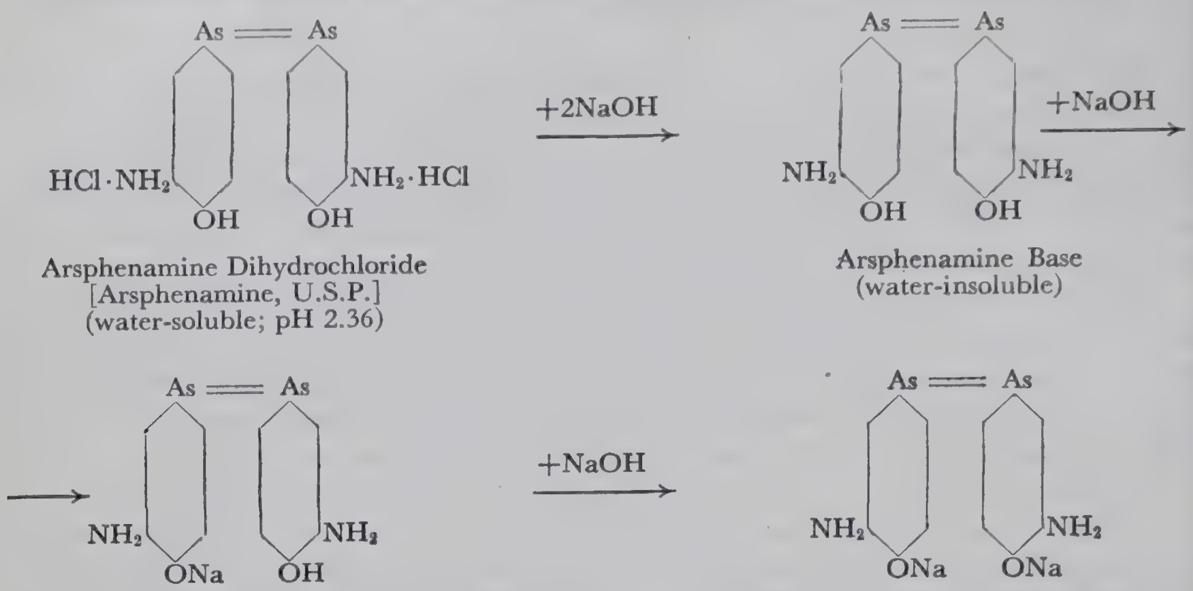
* *See* especially: The management of syphilis in general practice. Joseph Earle Moore and collaborators. Supplement No. 6 to Venereal Disease Information, 1938. Price 10 cents. U. S. Govt. Printing Office, Washington, D. C.

TABLE 47

CHEMICAL STEPS IN ALKALINIZATION OF ACID ARSPHENAMINE



Arsphenamine Dihydrochloride
[Arsphenamine, U.S.P.]
(water-soluble; pH 2.36)

Arsphenamine Base
(water-insoluble)

Monosodium Arsphenamine
(water-soluble; pH 10.64)

Disodium Arsphenamine
(water-soluble; pH 11.32)

Injection. The route of administration of arsphenamine is always intravenous. It must be injected slowly *by gravity* at a rate not exceeding 20 cc (0.1 gram) per minute. Extravasation of the solution into the subcutaneous tissues results in sloughing which in part can be prevented by immediate aspiration followed by the injection of physiological sodium chloride solution into the involved area.

Cannon (1939) described in detail a syringe method for the intravenous administration of alkalinized arsphenamine which requires a minimum of labor, time and equipment, avoids the cumbersome gravity method hitherto employed, and makes it practicable for the general practitioner to use arsphenamine in his daily practice. Reactions encountered with Cannon's method appear to be milder than those encountered with the gravity method.

Dosage. The average single dose of arsphenamine for adult males is 0.4 gram; for adult females, 0.3 gram. The upper limit of 0.6 gram per dose is not to be exceeded. In the treatment of *early syphilis,* arsphenamine is given in courses of one injection weekly for six to eight weeks, alternating *without rest periods* with courses of heavy metal therapy. This continues for 12 or even 16 months after all lesions have healed and the serology is negative. Thus between 25 and 30 injections, a total of eight to 12 grams of arsphenamine, are usually given in early syphilis in a period of 45 to 60 weeks.

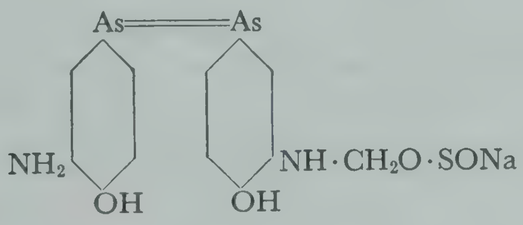
Advantages of Arsphenamine. Arsphenamine is the best known and the most efficient of all the arsphenamines. It is also the most stable drug of its group. Large amounts of the alkalinized solution can be made at once and will keep for three hours, which is an advantage for mass treatment in the clinic. Both its therapeutic potency and toxicity are well known and fairly uniform. Finally, the drug is relatively cheap.

Disadvantages of Arsphenamine. The proper preparation of arsphenamine solutions presents technical difficulties, and errors in technic have caused serious accidents. The injection requires a gravity apparatus, and cannot be made until one-half hour after the disodium salt has been prepared. Arsphenamine is somewhat more likely to cause gastro-intestinal reactions. Some patients are intolerant of the garlic odor and taste which it causes. Its tendency to thrombose veins, especially when dissolved in distilled water rather than in saline solution, makes it difficult to give to children, obese persons and others with veins difficult to reach. The use of arsphenamine is inadvisable in certain forms of late syphilis and is especially contraindicated in cardiovascular syphilis.

Neoarsphenamine

After the discovery of salvarsan, Ehrlich continued the search for a soluble arsphenamine which did not require alkalinization prior to use. Soon neosalvarsan was discovered, and within a few years it was widely employed in syphilotherapy. The drug is called neoarsphenamine in the United States and is official in the U.S.P. Synonyms for it are "neodiarsenol," "novarsenobenzol" and "914."

Chemistry. Neoarsphenamine is sodium 3,3 diamino 4,4 dihydroxyarsenobenzene methanal sulfoxylate, a derivative of arsphenamine. Its formula is as follows:



Neoarsphenamine

Neoarsphenamine, U.S.P., B.P., contains 19 to 22 per cent of arsenic in the trivalent form. It is a canary yellow powder which dissolves in water to give a yellow solution neutral to litmus. It is supplied in vacuum or nitrogen-filled glass ampules which should be kept in the ice box to prevent deterioration. Neoarsphenamine is less stable than arsphenamine and deteriorates in solution or on exposure to air to give toxic oxidation products.

Preparation and Administration. The ampule must be critically examined for cracks or deterioration of the contents. Above all, *an ampule of arsphenamine must not be mistaken for one of neoarsphenamine.* This error usually is fatal to the patient. The neoarsphenamine is sprinkled into sterile distilled water at room temperature. The amount of water used is from two to 10 cc per 0.1 gram of drug, but a total of 15 to 20 cc is usually employed for the average therapeutic dose. Shaking or agitation to effect solution is not allowable for it increases toxicity. Complete solution should occur within 10 minutes and only perfectly clear and transparent solutions should be injected.

Injection. In sharp contrast to arsphenamine, neoarsphenamine is injected as soon as the solution is prepared. It is not safe to use the drug if it has stood longer than 20 minutes. The drug is always given intravenously in adults. Injection is made slowly at the rate of not more than 0.1 gram per 30 seconds. If the solution contains 0.1 gram of drug in less than 10 cc, a slower rate of injection is used. Some physicians inject neoarsphenamine under the fascia of the scalp in babies with congenital syphilis.

Dosage. Neoarsphenamine is less toxic and contains less arsenic than does arsphenamine, and is given in correspondingly larger amounts. The average single dose for adult males is 0.9 gram; for adult females, 0.75 gram. These doses are also maximal doses. For early syphilis, neoarsphenamine is given in courses of one injection weekly for 10 to 12 weeks, alternating *without rest periods* with courses of heavy metals. This treatment continues for a year or more. It should be noted that the length of each course, as well as the size of the dose, is greater than for arsphenamine.

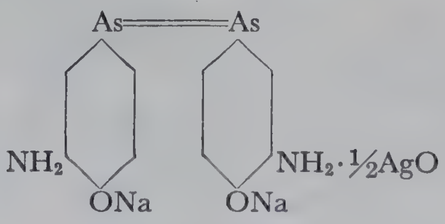
Advantages of Neoarsphenamine. Solutions of neoarsphenamine are considerably easier to prepare and administer than those of arsphenamine. No alkalinization is necessary; the solutions need not stand before use; and injection can be made by syringe. Neoarsphenamine causes fewer gastro-intestinal reactions. It is less irritant than arsphenamine and does not thrombose veins. Neoarsphenamine is said to have marked "tonic" effects, and is much more suitable than arsphenamine for cachectic, aged, weak or very young patients. It can also be employed in forms of late syphilis where arsphenamine is contraindicated.

Disadvantages of Neoarsphenamine. Neoarsphenamine is an unstable compound and different batches may vary appreciably in toxicity and therapeutic potency. The drug must be kept in the dark and on ice and must not be over six months old. Deterioration may occur in the ampule or in solution and slight errors in technic enhance the number and severity of untoward reactions. Like arsphenamine, it causes a garlic odor to which some patients object. A greater number of injections is required. Nitritoid crises are somewhat more frequent than with arsphenamine.

Silver Arsphenamine

Silver arsphenamine (silver salvarsan) was introduced in 1918 by Kolle, Ehrlich's successor. It rapidly found favor in many quarters as an efficient and relatively safe agent in syphilotherapy.

Chemistry. *Silver arsphenamine,* N.N.R., is an amorphous brownish black powder, readily soluble in water without shaking and forms a clear, deep-brown solution which is slightly alkaline to litmus. It contains 19 per cent of trivalent arsenic and 12 to 14 per cent of silver. The exact chemical linkage of the silver is unknown. It has been assigned by some to the secondary valencies of the arsenic and by others to the amino groups. Some believe it is a chemically homogeneous substance and others that it is an intimate mixture of arsphenamine and colloidal silver. It is marketed in sealed ampules as the sodium salt and has the following structural formula:



Silver Arsphenamine

Preparation and Administration. The ampule is inspected for defects, opened with sterile precautions and the contents sprinkled into sterile distilled water at room temperature. Five cc of fluid are used for each 0.1 gram of drug. Complete solution is effected without stirring but gentle rotation is permissible. Silver arsphenamine decomposes when exposed to the carbon dioxide of the air and oxidation also takes place more rapidly than with arsphenamine, but somewhat more slowly than with neoarsphenamine. Exposure or shaking of the solution increases toxicity. Solutions are allowed to stand up to but not longer than 20 minutes before using. Injections are always made intravenously, slowly and evenly. Three to four minutes are allowed for the injection. Only solutions which are perfectly clear (like black coffee) are to be employed.

Dosage. The average dose of silver arsphenamine for adults with early syphilis is 0.4 gram for males and 0.3 gram for females. It is given in courses of one injection weekly for eight to 10 weeks, and alternated *without rest periods* with courses of heavy metals. This treatment is continued for 12 to 16 months after the serology is negative and the visible lesions have healed.

Advantages. When administered as suggested, silver arsphenamine probably has the therapeutic value of neoarsphenamine. It is considerably less likely to cause gastro-intestinal or nitritoid reactions. The garlic odor which is often an objectionable feature of other arsphenamines is lacking with this drug. A decided advantage is the lack of irritation to veins, and thus thrombosis does not result from injection of silver arsphenamine. It can be given by the syringe method and solutions are readily prepared for use without alkalinization. The suggestion that silver arsphenamine may be of special value in neurosyphilis requires confirmation.

Disadvantages. Details of technic in the preparation of silver arsphenamine solutions must be closely observed to prevent increased toxicity and the solutions must be used within 20 minutes. The dark brown color of the solution may cause some difficulty for the inexperienced in ascertaining whether the needle has entered the vein and blood has been aspirated. Argyria may rarely occur if this chemical is given for a long period. Silver arsphenamine is not as well fortified by clinical experience as are the older arsphenamines, and therefore an authoritative comparison of this compound with others in respect to ultimate clinical outcome is impossible.

Silver Neoarsphenamine

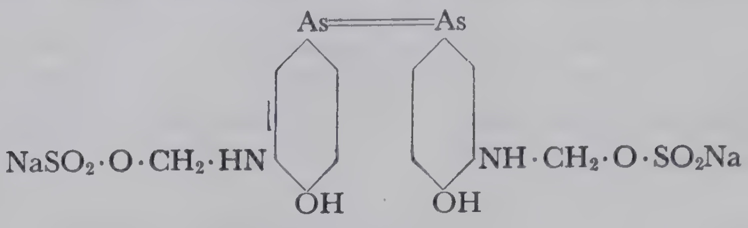
This compound is a silver derivative of neoarsphenamine and contains about 20 per cent trivalent arsenic and six to seven per cent silver. It is a grayish-green powder, soluble in water and prepared and administered in a manner exactly similar to that for silver arsphenamine. Solutions are brownish-black in color and must be injected immediately after being made in order to avoid toxic deterioration. The average single adult dose is 0.4 gram.

The *status* of silver neoarsphenamine cannot be accurately stated because the product has been used too little in the United States to allow a long range comparison with the better known arsphenamines. It is said to be quite effective and well tolerated and to have a better chemotherapeutic index than silver arsphenamine. Silver neoarsphenamine cannot be recommended to the general practitioner until more information is available concerning its efficacy and toxicity. The drug is not official and is not included in the N.N.R.

Sulfarsphenamine

This compound was developed by Voegtlin and associates (1922) at the Hygienic Laboratory of the United States Public Health Service. Its main advantage is that it can be given intramuscularly.

Chemistry. *Sulfarsphenamine,* B.P., N.N.R., is disodium 3–3′ diamino 4–4′ dihydroxyarsenobenzene N, N′-dimethylene sulfonate. It is a formaldehyde sulfoxylate derivative of arsphenamine and has the following structural formula:



Sulfarsphenamine

Sulfarsphenamine is a light yellow powder containing 19 per cent of trivalent arsenic. It is the most soluble of all the arsphenamines and in aqueous solution it is slightly acid to litmus. It remains stable in the ampule and resists oxidation in solution even when exposed to air for many hours.

Preparation and Administration. After inspection, the ampule is opened with sterile technic and distilled cool sterile water is added directly into the ampule to effect solution. For every 0.1 gram of sulfarsphenamine, 0.3 cc of water is added, but not less than a total of 1.0 cc is used. Solution should occur quickly and completely.

The route of injection is intramuscular. Due to its high solubility and lack of irritation, the drug is well tolerated by the tissues when in concentrated solution. Intravenous injection is possible but not recommended because the chemical is about twice as toxic by this channel. The highly concentrated solution suggested is injected deeply into the buttocks by the usual technic, but it cannot be given intravenously without danger of jelling and causing serious accident. For intravenous injection, the dose should be contained in 10 to 20 cc of solution.

Dose. The average single intramuscular dose for adults with early syphilis is 0.4 gram. The maximal allowable amount is 0.6 gram. In infants, the intramuscular dose is 10 to 25 mgm (average 15 mgm) per kg of body weight. A course for adults consists of not more than 12 injections (usually eight to 10) given at intervals of five to seven days. In early syphilis, this is alternated *without rest periods* with courses of heavy metals and continued for 12 to 16 months. A course of sulfarsphenamine for children consists of six to eight injections.

Advantages. Sulfarsphenamine is the only arsphenamine well tolerated by intramuscular injection. It is therefore useful in congenital syphilis of infants when intravenous injection is troublesome, as well as in some obese patients and others with inaccessible veins. It is easy to prepare and administer and is stable in solution and in the ampule, although lots from different manufacturers differ considerably in toxicity. Immediate reactions are less common than with other arsphenamines.

Disadvantages. The incidence of serious late reactions in adults is so high that sulfarsphenamine should not be employed if it is possible to use a potent antisyphilitic arsenical intravenously. Late toxic effects include nephritis, bone marrow and blood dyscrasias, exfoliative dermatitis and hemorrhagic encephalitis, all of which are serious. Fortunately, infants appear to be less susceptible to the untoward effects of the drug. The superiority of sulfarsphenamine remains to be proved and it is the least desirable member of the group when a choice of preparations is possible. Its use in adults has practically been abandoned. It should not be given intravenously.

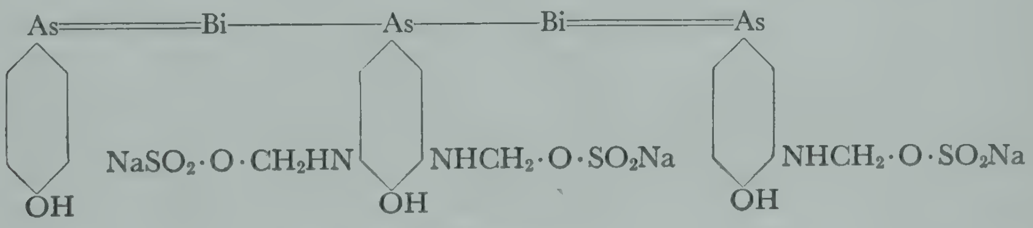
Trisodarsen

Trisodarsen (formerly called triarsen) has been suggested for use in syphilotherapy. It is the trisodium salt of 3–3′ diamino 4–4′ dihydroxyarsenobenzene N, N′ dimethylene sulfonic acid. It differs from sulfarsphenamine in having an additional sodium atom substituted for the H in the OH in position 4′. The chief advantage over sulfarsphenamine is that trisodarsen can be given intravenously. The product is too new to know all its therapeutic or toxic properties or to recommend its use. Satisfactory results with trisodarsen in the treatment of congenital syphilis have been reported by Givan and Villa (1939). The drug is not official and is not included in N.N.R. (*See* the Report of the Council, 1937, for the pertinent literature; also Stokes, 1937.)

Bismarsen

This chemical was produced in the United States by Raiziss and his collaborators and has been employed clinically since the middle 1920's.

Chemistry. *Bismarsen* (Sulfarsphenamine Bismuth), N.N.R., is bismuth arsphenamine sulfonate, a derivative of arsphenamine methylene sulfonic acid. It is a brownish-yellow amorphous powder, and dissolves readily in small amounts of water to form a slightly alkaline solution which oxidizes slowly when exposed to air. It contains 12 to 15 per cent of trivalent arsenic and 23 to 25 per cent of bismuth. The probable structural formula of bismarsen is as follows:



Bismarsen

Preparation and Administration. The ampule containing the drug is inspected in the usual manner and opened with precautions as to sterility. Sterile distilled water is added directly into the ampule to effect solution of the powder. One cc of fluid is used for each 0.1 gram of drug. The manufacturers of bismarsen supply ampules with the proper amount of sterile distilled water containing 0.25 per cent of butyn for local anesthesia. Injection is made intramuscularly only, the solution being deposited deep in the gluteal muscles. Bismarsen is ten times more toxic when given intravenously. The use of a dry needle helps to reduce pain.

Dose. The average dose of bismarsen for adults is 0.2 gram. Injections are given twice weekly or every four days, and a course in early syphilis consists of from 40 to 100 injections. Rapid absorption from the tissues is the reason for the short interval between injections.

Advantages. Bismarsen has the advantage that it can be given intramuscularly. It is fairly well tolerated by the tissues when properly injected. Immediate reactions are apparently fewer than when arsphenamines are employed intravenously. If they appear persistently after each injection, the patient is intolerant to bismarsen, and it should be discontinued. Serious delayed effects are less frequent than with sulfarsphenamine, the alternative intramuscular preparation.

Disadvantages. Bismarsen is the least effective of the arsphenamines in causing disappearance of the surface treponemes, in healing visible lesions, and in reversing the Wassermann reaction. There is some evidence of an increased incidence of neurorelapses following its use. Its clinical status is undetermined and employment of bismarsen should therefore be reserved for cases in which intravenous therapy with better known antisyphilitic arsenicals is impossible. The present day conception of continuous treatment of early syphilis with alternating courses of arsenic and bismuth or mercury cannot be satisfied by bismarsen which combines both arsenic and bismuth in the same drug. One must be on the alert for symptoms of bismuth as well as arsenic poisoning. The use of arsenic and bismuth together for long periods of time appears, theoretically at least, to increase the chance for "drug-fastness" of the treponemes.

Tryparsamide

Tryparsamide was derived from atoxyl by Jacobs and Heidelberger (1919). It was then studied biologically by Brown and Pearce (1919), and investigated clinically by Lorenz and Loevenhart (1923) who were particularly interested in the chemotherapy of neurosyphilis. *Tryparsamide is not an arsphenamine* and is radically different from all other antisyphilitic arsenicals. Its main use is in the treatment of late central nervous system syphilis, and in trypanosomiasis. A detailed review of tryparsamide in syphilotherapy has been presented by Hinrichsen (1939).

Chemistry. *Tryparsamide,* U.S.P., B.P., is the sodium salt of phenylglycineamide-4-arsonic acid. It is a white, stable, crystalline substance and contains about 25 per cent of arsenic in the *pentavalent* form. The chemical is quite soluble in cold water and forms a solution neutral to litmus. It is not oxidized by exposure to air either in the ampule or in solution. The structural formula of tryparsamide is given on page 736.

Preparation and Administration. The required dose of tryparsamide is dissolved in 10 to 20 cc of sterile distilled water. Exposure and agitation of the solution do not increase the toxicity. The solution is injected intravenously by the syringe method, and the rate of injection is not important. In patients with inaccessible veins, the drug can be given intramuscularly in three cc of water.

Dosage. Tryparsamide is given to adults in doses ranging from one to three grams, the latter being the usual and maximal amount. A course consists of 12 or more weekly injections but as many as 100 consecutive weekly injections may occasionally be given in neurosyphilis.

Advantages. Tryparsamide has particular value in the treatment of central nervous system syphilis, especially early paresis, either prior or subsequent to malariotherapy. The drug is easy to administer and its use is singularly free of immediate reactions and the delayed toxic effects observed after the use of arsphenamines. It does not cause dermatitis or injury to the bone marrow. In addition, it has a salutary "tonic" effect on patients. In fact, failure to gain weight after the administration of tryparsamide is of poor prognostic import. Approximately 50 per cent of patients with general paresis show clinical arrest or improvement after the use of the drug.

Disadvantages. Tryparsamide has no value in syphilis unless there is central nervous system involvement, and therefore should not be used in early syphilis. Although the chemical is highly trypanocidal, it is not treponemicidal and has practically no effect on surface organisms. Also it is valueless for healing visible lesions or reversing a positive serology. Tryparsamide, although it rarely causes constitutional reactions, does produce blindness in a certain number of patients. It is apparently directly toxic to the optic nerve and therefore is contraindicated in those who have pre-existing optic damage or atrophy. This specific toxicity for the optic nerve appears to be connected with the substituted amino group in the para position to the arsenic (Young and Loevenhart, 1924). The propensity for visual damage applies to both trivalent and pentavalent arsenicals, but those compounds with a substituted amino group in the ortho or meta position are apparently free of this danger. The details of tryparsamide poisoning are discussed later.

Atoxyl

Atoxyl was the original organic arsenical to be tried in experimental trypanosomiasis. The investigations of Thomas of Liverpool in 1905 proved the compound to be more effective than inorganic arsenic. This work attracted the attention and stimulated the interest of Ehrlich whose subsequent discoveries established the chemotherapy of syphilis. Atoxyl is *sodium arsanilate,* the structural formula of which is given on page 736. It is a pentavalent organic arsenical closely related to tryparsamide and carbarsone. The drug is not official and is not included in N.N.R. The name "atoxyl" serves as a reminder that this drug was once thought to be non-toxic. In addition to having the general toxic propensities of all organic arsenicals, the drug is especially dangerous because of the optic injury and blindness which result from its use. Here again, it is believed that the amino group in the para position to the arsenic on the benzene ring accounts for this peculiar affinity for the optic nerve.

Atoxyl was at one time employed for syphilis but has been abandoned as too dangerous and ineffective. Its sole use today is for *African sleeping sickness,* in which disease the drug apparently is quite an efficient trypanocide. Atoxyl is given only hypodermically, and the dose is 0.2 gram every other day. This amount may gradually be increased to 0.6 gram, but the total amount injected in one course should not exceed 6.0 grams. The patient's vision must be observed carefully in a manner similar to that described for tryparsamide medication.

Acetarsone

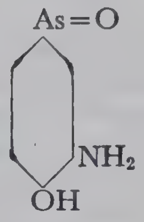
Acetarsone (stovarsol, spirocide), N.N.R., is an organic pentavalent arsenical, the structural formula of which is given on page 736. The drug is employed as an antisyphilitic and amebicide. It is given orally and thus has an advantage over arsenicals which must be administered parenterally, especially in the treatment of children with congenital syphilis. This advantage, however, does not outweigh the toxicity of the compound and the rather poor results obtained with it. The chemical cannot be recommended for the treatment of any form of syphilis, more effective and less toxic agents being available (*see* page 998). The value of acetarsone in the treatment of *amebiasis, sarcoid* and *Trichomonas vaginalis vaginitis,* and its general pharmacology and status are discussed in the chapter on amebicidal agents.

Arsenoxide (Mapharsen)

Arsenoxide was originally investigated by Ehrlich and Hata but pronounced too toxic for clinical use, the high therapeutic efficiency of the drug not being appreciated. The chemical remained of great theoretical interest, however, because it was believed to be the oxidation product through which the arsphenamines exerted their spirocheticidal action in the body.

After several years of careful laboratory and clinical research on the antisyphilitic use of arsenoxide, cautious reports of its value began to appear (Tatum and Cooper, 1932; 1934) and the drug was released for study to the Cooperative Clinical Group.* The available evidence indicates that this drug is one of the most promising arsenical treponemicides for syphilotherapy.

Chemistry. The term "arsenoxide" is really a generic one, but it is used in clinical literature to signify a particular chemical—meta-amino parahydroxy phenylarsine oxide. From the first letters in the component parts of this chemical name is derived the term "mapharsen." *The drug is not an arsphenamine,* but represents a partial oxidation product of arsphenamine. Its structural formula is as follows:



Mapharsen

Mapharsen, N.N.R., contains 29 per cent of *trivalent* arsenic and is marketed as the hemi-alcoholate in nitrogen-filled ampules. It is a fluffy hygroscopic powder which is quite stable in the dry state. After contact with air or moisture, it gradually darkens. Ampules of mapharsen contain an amount of sodium carbonate which exactly neutralizes the acid salt, and sufficient sucrose to make solutions isotonic with blood. Every lot is tested for chemical purity and toxicity. The sealed ampules keep indefinitely. The physical and chemical properties of arsenoxide are such that, in contrast to the arsphenamines, the drug is neither precipitated by tissue fluids, nor does it agglutinate or hemolyze red blood cells.

Preparation and Administration. For preparation of single doses, the ampule is opened with sterile precautions and two cc of sterile water are added to the drug in the ampule. Solution occurs quickly with effervescence. The solution is then drawn into a syringe and enough additional sterile water added to make a total volume of 10 cc. For multiple doses, solutions can be prepared in beakers. The pH of the mixture is practically neutral. Stirring to insure solution is permissible and desirable. Aeration, exposure for hours, or even boiling (for one minute) does not increase the toxicity or decrease the therapeutic value of mapharsen solutions. Toxicity may actually be lessened somewhat by exposure. After prolonged standing, a brown color appears but this is of no importance.

Injection is made intravenously and rapidly by syringe. The entire dose should be given within 15 to 30 seconds, a procedure which lessens pain in the arm and decreases the possibility of thrombosis from vascular irritation.

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* The Cooperative Clinical Group consists of the heads of the syphilis clinics of The Johns Hopkins University, Mayo Clinic, University of Michigan, University of Pennsylvania and Western Reserve University, and of representatives of the United States Public Health Service.

Dosage. The dose of mapharsen is one-tenth that of arsphenamine. The average initial adult dose is 40 mgm for males and 30 mgm for females. The average maintenance dose is 60 mgm for men and 40 mgm for women. The courses in early syphilis consist of eight to 10 weekly injections and are alternated with heavy metals *without rest periods.* In some clinics, the course of mapharsen consists of *two* injections weekly for 10 weeks. The initial dose for children is one-half mgm per kg, and this may later be increased to one mgm.

It is clear that the absolute amount of arsenic given in a course of mapharsen therapy is only about one-tenth of that given in a course of arsphenamine. Cumulative arsenical poisoning is therefore much less likely. The animal studies of Wright and collaborators (1937) confirm this fact. Rosenthal (1932) showed that only about one-tenth of arsphenamine is converted to arsenoxide in the body. This agrees with the data on the relative effective dosages of arsphenamine and mapharsen. Although the toxicity of mapharsen (for animals) is about six times greater than that of arsphenamine, its clinical efficiency on the basis of arsenic content is likewise about six times as great (Roth and Creswell, 1937).

Advantages and Clinical Status. Mapharsen is easy to administer. It requires no special precautions in preparation, can be given by syringe, need not be alkalinized, and can be injected rapidly as soon as the solution is made. Large amounts of solution may be prepared for mass treatment in the clinic because the solution keeps for hours and even becomes less toxic upon standing. Mapharsen is also a pure chemical substance which is uniform in constitution. Thus it can be chemically as well as biologically standardized. This insures constancy of therapeutic and toxic properties. It is neutral in solution, crystalloidal rather than colloidal, and the reactions due to the physical properties of the arsphenamines are thus absent. The dose of mapharsen is much smaller than that for arsphenamines and thus less arsenic need be handled by the body.

Although all the evidence is not yet available, mapharsen appears to be superior to neoarsphenamine and approaches arsphenamine in the ability to cause disappearance of surface treponemes, heal surface lesions and effect reversal of the Wassermann reaction. It is directly spirochetocidal and is not dependent on intermediate breakdown products for its activity. In fact, it is believed by some to be the substance by means of which the arsphenamines act as spirocheticides and trypanocides. In rat trypanosomiasis and rabbit syphilis, the drug has a higher therapeutic index than neoarsphenamine.

Mapharsen is well tolerated in the body. Gastro-intestinal upsets are fewer and the drug is less likely to make the patient ill. The patient is thus more willing to continue therapy. Nitritoid reactions to mapharsen do not occur. It can often be used in full doses in patients intolerant to the arsphenamines (Jordan and Traenkle, 1937) and appears to cause a lower incidence of serious skin and visceral reactions. There is some evidence that excretion may be more rapid than that of the arsphenamines (80 per cent excreted within one week) and that mapharsen may therefore be given twice weekly.

The relative safety of mapharsen is seen in the fact that there was no reported fatality during the first three million injections. In 1939, the first death from mapharsen was recorded (Simon and Iglauer, 1939). The usual figures given for deaths from the arsphenamines are as follows: Parsons (1937, 1939), in an analysis of the treatment of syphilis in the United States Navy between 1925 and 1938, reported one death in approximately

42,000 injections of arsphenamine as compared to one in approximately 28,000 of neoarsphenamine. Indeed, the Cologne Commission reports an aggregate death rate of one per 11,289 injections of the arsphenamines. The same commission gives an incidence of dermatitis of one case in 1850 injections of arsphenamine and one in 5370 of neoarsphenamine; of jaundice, one in 2100 injections of arsphenamine and one in 6364 of neoarsphenamine. These figures contrast with those obtained from the combined data of several reports on mapharsen as follows: dermatitis, one case in 6300 injections; jaundice, one in 21,600 (Wieder, 1938). The aforementioned data are in essential agreement with those of Parsons (1940) who found, in the study already cited, that the ratios of non-fatal reactions to the number of injections of the various antisyphilitic arsenicals as follows: arsphenamine, 1:989; neoarsphenamine, 1:1335; sulfarsphenamine, 1:1140; mapharsen, 1:7036; tryparsamide, 1:14,514. Furthermore, evidence is accumulating that mapharsen is well tolerated in cardiovascular syphilis, elderly patients, those with tuberculosis, etc. For example, Gruhzit and coworkers (1936) gave 75,589 injections to 4841 syphilitic patients and noted no severe complications such as anemia, jaundice, exfoliative dermatitis, hemorrhagic encephalitis or severe nitritoid reactions.

The direct parasiticidal action of mapharsen permits its use in other spirochetal diseases, especially in *Vincent's angina* where it can be employed as the dry powder or in 0.5 to 1.0 per cent solution (Duehr and associates, 1936).

Disadvantages. Inasmuch as mapharsen has been in use for only a few years, it is not yet possible to compare it with the older drugs in regard to ultimate clinical outcome. If the evidence from early syphilis offers an index of what may be expected, mapharsen will probably compare favorably with arsphenamine itself. However, only years of careful observation of a large number of patients will answer this important point. The remaining disadvantages of mapharsen are minor ones shared by other antisyphilitic arsenicals. Irritation of veins can be lessened by rapid injection. The garlic odor is still present but not very disagreeable. The usual precautions are necessary to prevent Jarisch-Herxheimer reactions.

PHARMACOLOGY OF THE ARSPHENAMINES

The pharmacology of the various arsphenamines is sufficiently similar so that these drugs may be discussed together. Salient differences between the members of the group will be described as occasion arises.

Significant Chemical and Physical Properties of the Arsphenamines. The arsphenamines all contain arsenic in the trivalent form and this appears to be essential for their spirocheticidal action. The important feature of the arsphenamine structure is the double bond linkage between two atoms of arsenic as follows: $R \cdot As{=}As \cdot R$, in which R is the benzene ring with an amino group attached in the meta and a hydroxy group in the para position to the arsenic. Isomers of arsphenamine are less spirocheticidal. It must be assumed, therefore, that the amino and hydroxy groups are optimally placed in the benzene nucleus and lend to arsphenamine the necessary physical and chemical properties for efficient parasiticidal action.

Oxidation of arsphenamine causes the splitting of the $R \cdot As{=}As \cdot R$ linkage to form arsenious oxide, $R \cdot As{=}O$ (arsenoxide), which is much more toxic. This occurs readily in an alkaline medium. Thus, the dihydrochloride and base of arsphenamine are not readily changed but solutions of the sodium salts are easily oxidized. For this reason, solutions containing alkalinized arsphenamine should never be agitated or aerated. The rôle of the oxidation products of arsphenamine on the biological activity of the drug will be discussed later. The poor solubility of arsphenamine base is changed by chemical substitution in the amino groups. For this reason, neoarsphenamine and sulfarsphenamine are very soluble and need not be alkalinized to effect their solution.

Arsphenamine itself has many properties which resemble those of colloids and it is also amphoteric in character due to its amino and phenolic hydroxy groups. It thus has properties in common with proteins (*see* Voegtlin, 1925, for review of the literature). The physical properties of arsphenamine are probably the basis for some of the untoward reactions after the intravenous injection of its solutions. The colloidal character of the drug may account for some features of the nitritoid crises and shock-like responses, and the pH of the injected solution is also an important factor. Alkaline solutions may cause pulmonary vasoconstriction and a fall in systemic arterial pressure. For these reasons arsphenamine solutions are well diluted and injected very slowly. Acid arsphenamine causes multiple minute pulmonary emboli by precipitation of plasma proteins and especially by the agglutination of red blood cells. Neoarsphenamine is not so likely to cause immediate circulatory disturbances because it is more soluble at the pH of the blood, less alkaline and better dispersed in solution. The same is true of sulfarsphenamine except that it is acid in reaction.

Absorption, Fate and Excretion of the Arsphenamines. *Absorption.* Arsphenamine solution cannot be injected hypodermically because it irritates tissue and the drug precipitates out as the free base, the slow oxidation of which causes further local injury. Neoarsphenamine and silver arsphenamine, if injected hypodermically, are also oxidized to products injurious to tissue. These drugs must therefore be given intravenously. Sulfarsphenamine is oxidized less readily, is non-irritating and is readily absorbed from the tissues. Its preferred route is therefore intramuscular. Arsphenamines are less adequately absorbed from subcutaneous than from intramuscular depots and very poorly absorbed from the intestinal tract.

Fate and Distribution. Arsphenamines disappear from the circulating blood very rapidly after intravenous injection. Most of the chemical is removed within a few minutes, and after three to four hours only traces can be found. The drug which disappears from the blood is stored in the tissues. On the basis of weight, the liver and spleen contain more of the arsphenamine than other organs. The liver, due to its size and affinity for the chemical, apparently is the chief storehouse for the arsphenamines. The very high glutathione content of the liver may be related to its power for binding arsenic. The rôle of glutathione in the chemical fate of arsphenamines will be discussed. The liver also appears to be important in changing the arsphenamines to more active oxidation products (arsenoxide) and slowly releasing the highly treponemicidal substances to the circulation. That fraction of arsphenamine which is not eliminated within the first week is stored in a non-treponemicidal form in the body for slow ultimate excretion. This stored chemical, however, is still toxic and capable of causing cumulative arsenical poisoning.

Arsenic is distributed to all tissues and fluids of the body. The skin and bones may retain small amounts for long periods of time. The placenta and fetal tissues also receive their share of arsphenamine, a matter of significance in the treatment of syphilis during pregnancy.

Central Nervous System. The high incidence and seriousness of central nervous system syphilis have focused attention on the penetration of arsphenamine into the *brain* and *cerebrospinal fluid.* The nervous tissue appears to contain little arsenic. The spinal fluid, however, has a higher concentration of arsphenamine than the blood. Various arsphenamines, arsenoxide and tryparsamide have been compared both in patients and animals for their ability to penetrate into the nervous system. This has been done by actual arsenic estimations and by determining the curative effect of these drugs after intradural inoculation of trypanosomes or spirochetes. The results in man indicate that more arsenic is found in the spinal fluid after the administration of silver arsphenamine than after the other chemicals. This has been interpreted as signifying the special usefulness of silver arsphenamine in neurosyphilis, but the clinical results are not conclusive. Furthermore, tryparsamide which has proved its worth in the therapy of neurosyphilis, causes the least accumulation of arsenic in the spinal fluid. Sterilization of infections produced in animals by intradurally injected organisms appears to be more readily accomplished by sulfarsphenamine, atoxyl and tryparsamide than by massive doses of arsphenamine itself or arsenoxide (Voegtlin and coworkers, 1923). In Table 48, compiled by Moore (1933) from the work of Cornwall and collaborators (1931) and Fordyce and coworkers (1923 *et seq.*), are presented the clinical data available on the distribution of arsenic in the cerebrospinal fluid.

TABLE 48

ARSENIC IN THE SPINAL FLUID *

DRUG	PERCENTAGE OF PATIENTS SHOWING ARSENIC IN CEREBROSPINAL FLUID	AVERAGE AMOUNT OF ARSENIC PRESENT, IN MGM. PER 100 GM. OF CEREBROSPINAL FLUID
Arsphenamine	77.5	4
Neoarsphenamine	77	5 to 10
Silver arsphenamine	70 to 85	11.5 to 12.5
Tryparsamide	100	2 to 2.5

* From table compiled by Moore (1933).

The present evidence, therefore, indicates that clinical rather than experimental results must be the basis of selection of arsenicals for neurosyphilis. The efficacy of tryparsamide may be related to its greater ability to penetrate membranes, which in turn is due to its content of pentavalent rather than trivalent arsenic and to its lack of colloidality. After tryparsamide, however, the spinal fluid of patients contains active trivalent arsenic, the concentration of which is highest about 40 hours after injection of the drug. Trypanocidal potency of the spinal fluid does not necessarily parallel the concentration of arsenic, being maximal 14 hours after the administration of the tryparsamide (Hawking and associates, 1937). Clinically, attempts are made to increase the permeability of the blood-cerebrospinal fluid barrier on the premise that an elevated arsenic content of the spinal fluid is important. For this purpose, fever therapy, spinal drainage and other measures are employed with arsenicals.

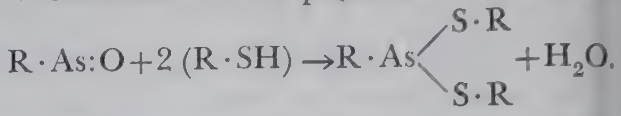
Excretion. Excretion of arsenic after the intravenous injection of arsphenamines is largely by way of the urine and feces. Small amounts of arsenic are also eliminated in the saliva, milk and sweat. Excretion is highest during the twenty-four hours following the injection. Thereafter, smaller and smaller increments are eliminated. About 50 to 70 per cent is excreted within one week and this is a determinant of the weekly interval between injections in patients. Traces can be detected for 14 days or longer after a single dose.

Urinary excretion starts within a few hours after the administration of arsphenamines. Diuresis does not increase the amount of element eliminated. About eight to 13 per cent of the injected arsenic is found in the urine within the first three days. More neoarsphenamine and tryparsamide is excreted by way of the urine than is true of arsphenamine itself. *Biliary excretion* also starts shortly after the injection of an arsphenamine. More than half the total of the eliminated arsphenamine appears in the stool in the first week after a single dose. More arsphenamine than neoarsphenamine is excreted in the bile and the fecal excretion of arsphenamine is four to ten times greater than the urinary. The important rôle of the liver in the metabolism and storage of the arsphenamines is reflected in this biliary excretion. That the arsenic present in the feces is due to biliary excretion is proved by the fall in fecal arsenic in animals with biliary fistulas. Ligation of the ureters enhances the opportunity for poisoning from those arsenicals mainly excreted by the urine—neoarsphenamine and tryparsamide. Ligation of the biliary ducts increases the toxicity for arsphenamine which depends largely on the bile for its excretion. These examples serve to illustrate once again the importance of the patency of the channels of excretion in determining the safety of a drug.

The chemical form in which the arsphenamines are excreted is not fully understood. Some of the arsenic is in inorganic form and another perhaps larger portion gives the reaction for the aromatic amino groups of arsphenamine. The double bond linkage in $R \cdot As = As \cdot R$ is largely broken by partial oxidation. This forms the arsenoxide stage, $R \cdot As = O$. Further oxidation may then occur to the pentavalent form before excretion takes place.

The Mechanism of the Parasiticidal Action of the Arsphenamines. The mechanism by which the arsphenamines kill trypanosomes and spirochetes has been the subject of considerable investigation. The pertinent earlier literature has been reviewed by Voegtlin (1925), Rosenthal (1932) and Eagle (1938). The original view of Ehrlich that these drugs are directly lethal to spirochetes and trypanosomes was soon challenged by experiments which seemed to indicate that direct contact *in vitro* between the parasites and very high concentrations of drug reduced neither their motility nor growth. The conviction gradually evolved that the tissues of the host were necessary for the chemotherapeutic action of the arsphenamines. The nature of the reaction between the body and the drug to produce death of the invading parasites has been elucidated especially by the investigations of Voegtlin, Smith, Rosenthal and their associates. This work shows that the arsphenamines must first be converted to a partial oxidation product—arsenoxide—before lethal effects on the parasite are noted. The evidence for this view is worthy of closer inspection.

Arsenicals of the arsenoxide character ($R \cdot As = O$) are trypanocidal *in vitro* in very low concentrations, comparable with those obtainable in tissues during the clinical use of the arsphenamines. When an arsphenamine is administered to animals infected with spirochetes or trypanosomes, a latent period of several hours intervenes before the parasites are cleared from the blood. Other arsenicals, such as the arsine of arsphenamine ($R \cdot AsH_2$), which are capable of oxidation to arsenoxide also exhibit spirocheticidal action characterized by a latent period. On the other hand, injection of arsenoxide, or arsphenamine which has been allowed to undergo partial oxidation in solution before injection, abolishes or materially shortens the latent period for destruction of the organisms. This is shown in Figure 88. These facts suggest strongly that arsphenamines are changed by oxidation in the host to yield potent parasiticidal agents and that this transformation takes time.

If an oxidation product of the arsphenamines is responsible for the activity of the drugs, it still remains to be demonstrated how it selectively kills the parasite. If reduced glutathione ($R \cdot SH$) is added in minimal amounts to an *in vitro* suspension of trypanosomes, they are protected from the highly lethal effects of arsenoxide. The trypanosomes can be shown by the nitroprusside test to contain some type of sulfhydril compound similar to glutathione. It is believed that arsenoxide combines with this sulfhydril to oxidize it to a form incapable of performing an important rôle in the respiratory metabolism of the parasite which thereupon dies. The interaction is as follows:  $R\cdot As{:}O + 2\,(R\cdot SH) \rightarrow R\cdot As\begin{matrix} S\cdot R \\ S\cdot R \end{matrix} + H_2O.$

Thus, when glutathione and certain other sulfur-containing substances, such as cysteine, thioglycollic acid, thiolactic acid, etc., are added to suspensions of the organisms, they combine with arsenoxide and protect the parasite against the drug. This drug-binding power can also be demonstrated *in vivo* by injecting the sulfur compounds in an infected animal prior to a minimal effective dose of arsenoxide. The parasites start to disappear only after a significant latent period (Figure 88), and if a larger amount of protective sulfhydril is given the organisms are not killed. Ehrlich showed that trypanosomes exposed *in vitro* to arsphenamine did not die but lost their pathogenicity for mice. This and other evidence suggest that the drug is fixed in the parasite. Conversion of the fixed arsphenamine into a lethal oxidation product presumably does not occur until the parasites are injected into an animal, whereupon arsenoxide is formed by the tissues at the site of inoculation (Voegtlin, 1925).

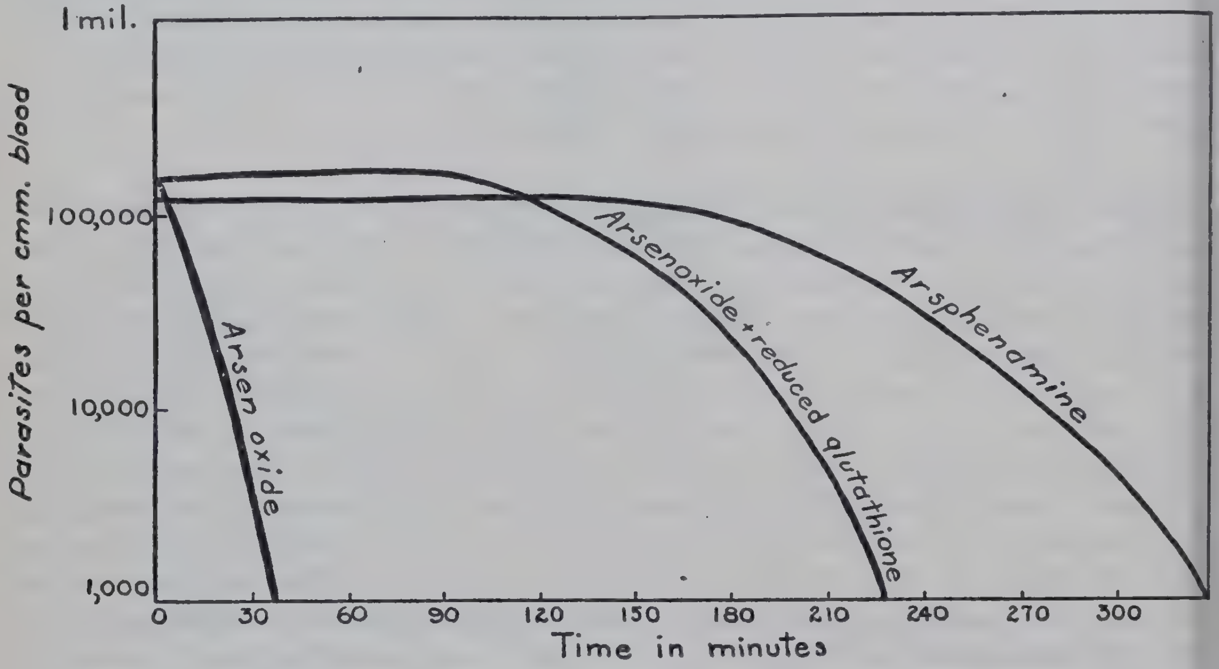
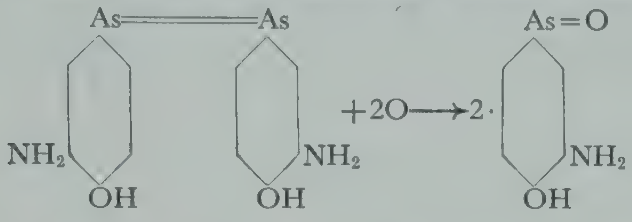


FIGURE 88. *The parasiticidal effect in rats with trypanosomiasis of arsphenamine, arsenoxide, and arsenoxide plus reduced glutathione.*

Note the long latent period before the trypanocidal action of arsphenamine is manifest in contrast with the almost immediate effect of arsenoxide. The administration of reduced glutathione greatly delays the onset of parasiticidal action of arsenoxide. (After Voegtlin, 1925. Courtesy of *Physiological Reviews.*)

That a conversion of the arsphenamine to oxidation products of the arsenoxide character actually occurs is suggested by a number of observations. Toxic doses of arsphenamines injected into an animal cause the appearance of symptoms only after a definite latent period. If solutions of arsphenamines are exposed to allow oxidation, they become highly toxic and cause acute symptoms without a latent interval. The relation between the effective clinical doses of arsphenamine, neoarsphenamine and mapharsen also suggests that the arsenic of the arsphenamine is changed to the arsenoxide form. Arsphenamine itself, if prevented from oxidation, is not toxic when tested on isolated organs. In animals, toxic symptoms from arsphenamines can be delayed or prevented by the prior injection of substances known to bind arsenoxide, namely, reduced glutathione. Therefore, despite the fact that arsenoxide has not yet been isolated from tissues, it appears likely that arsphenamines are converted into this oxidation product in the body. This conversion is presented in the following schematic formula:



A considerable amount of the evidence presented for the arsenoxide theory of arsphenamine action has been derived from experiments on trypanosomes. It is of interest, therefore, that Eagle (1938) has reinvestigated the spirocheticidal effects of the arsphenamines on *Spirocheta pallida* (Nichols strain and strains recently isolated from human lesions). Using concentrations of arsphenamine, neoarsphenamine and mapharsen compatible with those obtained in tissues after clinical doses, he showed that the organisms were immobilized *in vitro*. Sulfarsphenamine, on the other hand, was relatively inactive. More significant was the finding that death of the spirochetes had apparently occurred as indicated by the non-infectiousness of the spirochetes for rabbits, demonstrated both by testicular inoculation and lymph node transfer. Serum and tissue mash added to the *in vitro* mixture of arsphenamine and parasite appeared to inhibit rather than hasten the spirocheticidal effects, presumably by binding the drug. Eagle entertained the possibility that arsphenamine may be directly lethal to spirochetes without the necessity of conversion to an oxide. He was careful to point out, however, that the possibility of oxidation of arsphenamine under the experimental conditions had not been excluded and that this *in vitro* evidence may not be transferable to the *in vivo* therapeutic action of the arsphenamines.

In a later investigation, Eagle (1939) retested the *in vitro* antispirochetal potency of the arsphenamines and mapharsen under anaerobic conditions. Whereas the activity of mapharsen was unaffected by the removal of molecular oxygen, neoarsphenamine was negligibly spirocheticidal when dissolved and tested under pure nitrogen. This is in sharp contrast to the marked potency of neoarsphenamine in the presence of oxygen. Oxygen made the drug actively parasiticidal within three to five minutes and did not require the presence of tissue derivatives to do this. Commercial arsphenamine and silver arsphenamine proved to be intermediate between mapharsen and neoarsphenamine in that a small residual amount of antispirochetal activity remained in the absence of oxygen. It was estimated that two-thirds of the potency of arsphenamine and seven-eighths that of silver arsphenamine was due to oxidation products. In the case of arsphenamine, the residual activity appeared to be accounted for by the presence of an impurity such as arsenoxide or an arsenoxide-like substance. Eagle also noted that sulfhydril compounds added in sufficient excess almost completely abolished the antispirochetal effects of the arsphenamines and mapharsen. It would appear from Eagle's work that the antisyphilitic arsenicals are active *in vitro*, but especially by virtue of oxidation products of the arsenoxide type, that oxidation can be accomplished without the intervention of tissue, and that the drugs may be spirocheticidal because of an affinity for the sulfhydril groups of the parasites.

Mechanism of Tissue Toxicity of Arsphenamines. It has been suggested by Voegtlin and coworkers that the same mechanism by which the arsphenamines are lethal to parasites is apparently concerned in their toxicity for the tissues of the host. Glutathione is important in the transport of hydrogen and functions in this manner in tissue respiration. By binding reduced glutathione, as indicated in the equation given above, the arsenoxide formed from arsphenamines causes cell injury and even death. In keeping with this premise, it has been demonstrated that reduced glutathione and similar SH compounds can protect animals from fatal doses of arsenoxide, as can also the prior feeding of amino acid precursors of glutathione (glutaminic acid and cystine). Thus, as Voegtlin (1925) has concluded, ". . . glutathione in its reduced form is a physiological antidote against arsenoxide and that the action of arsenic upon protoplasm is essentially due to an interference with the normal functioning of glutathione in the oxidation-reduction phenomena of the tissues."

Selective Action of Arsenoxide on Parasites as Compared with Tissue Cells of the Host. If the same fundamental mechanism underlies the toxicity of arsenoxide for the spirochetes and the tissues of the host, the question arises why the host is more resistant to the arsphenamines than are the parasites. The answer to this question is unknown but it has been suggested that mammalian tissue may oxidize arsenoxide to non-toxic and readily excreted pentavalent compounds more readily than do unicellular organisms, or that the latter may be more permeable to arsenoxide. It is also possible that the sulfhydril component of the respiratory system of spirochetes is more susceptible to linkage with arsenoxide. In any event, the difference between the responses of tissue cells and parasites to the arsphenamines most likely is purely quantitative.

Indices of Therapeutic Efficiency of the Arsenicals. The relative therapeutic potency of the arsphenamines can be measured in a number of ways. For convenience, the curative effect in experimental trypanosomiasis offers a ready index for comparison. This is more feasible than the laborious use of syphilitic rabbits which necessitates lymph gland transfer to normal rabbits to prove the sterilizing action of an arsenical. Therefore, the *preliminary* testing of arsenicals on rats infected with *T. equiperdum* is commonly employed. It is to be noted, however, that all the arsphenamines used clinically are highly trypanocidal, and a high therapeutic index in trypanosomal diseases does not necessarily signify a high spirocheticidal value. For example, tryparsamide ranks high in its lethal action against trypanosomes but is ineffective against spirochetes. Testing on trypanosomes, however, serves in some measure the useful purpose of controlling the therapeutic potency of new supplies of known antisyphilitic drugs. For the relationship between the spirocheticidal and trypanocidal activities of the arsphenamines, mapharsen and tryparsamide and their therapeutic effectiveness, the interested reader is referred to the reports of Probey (1939) and Kolmer and associates (1940).

Chemotherapeutic Ratios. The determination of the chemotherapeutic ratios of the arsphenamines requires that host toxicity as well as parasiticidal effects be known. Despite the fact that the arsphenamines are chemical entities, it is necessary to examine each manufactured lot for its toxic properties. This is done under the auspices of the National Institute of Health by means of a standard test on rats. Unfortunately, the therapeutic potency is not similarly subjected to continuous rigorous examination.

In Table 49, from data presented by Moore (1933), are depicted the experimental and clinical figures from which the margins of safety of the antisyphilitic arsenicals are calculated. In this table, the eighth column contains the maximal tolerated dose in animals in grams per kg. Assuming that this figure also holds for man, the ratio of therapeutic to toxic dose (last column) can be calculated on the basis of the usual therapeutic doses given to a 60 kg adult. All the arsphenamines show approximately the same range of safety on this basis, and apparently the single lethal dose for man is about 20 to 30 times as large as the average therapeutic dose. All arsenicals used in syphilis thus have a wide margin of safety. The seemingly greater safety of bismarsen is due to the use of small doses to prevent immediate reactions. This is counterbalanced by more frequent injections of the drug. The figures in Table 49 indicate a wider variation in the toxic doses of neoarsphenamine and sulfarsphenamine than of the other drugs, a reflection of the greater chemical variability and toxicity of these two agents as supplied commercially by different manufacturers or even by the same manufacturer.

TABLE 49

TOXIC AND CURATIVE DOSES AND MARGINS OF SAFETY OF COMMONLY EMPLOYED ANTISYPHILITIC ARSENICALS*

DRUG	RABBIT SYPHILIS			TRYPANOSOME INFECTIONS (mouse or rat)			MAXIMUM TOLERATED DOSE GM./KG. IN ANIMALS	AVERAGE MAXIMUM THERAPEUTIC DOSE IN GRAMS. (60 KG. MAN)	RATIO OF THERAPEUTIC TO TOXIC DOSE
	Tolerated Dose Mgm-/Kg.	Curative Dose Mgm/Kg.	Therapeutic Index	Tolerated Dose Mgm/Kg.	Curative Dose Mgm/Kg.	Therapeutic Index			
Arsphenamine	100 to 200	10 to 15	1:7 to 1:12	100 to 140	3 to 8	1:12 to 1:40	0.140	0.4	1:21†
Neoarsphenamine	225 to 350	20 to 40	1:5 to 1:17	200 to 375	4 to 10	1:20 to 1:90	0.375	0.9	1:25
Silver arsphenamine	100 to 115	4 to 10	1:10 to 1:25	130 to 170	2 to 11	1:11 to 1:80	0.170	0.3	1:34
Sulfarsphenamine	275 to 400	10 to 22	1:10 to 1:20	210 to 320	16 to 32	1:10 to 1:20	0.320	0.6	1:30
Bismarsen	300 (?) (I.M.)**	20	1:15	300 (I.M.)**	15	1:20	0.300	0.2	1:90
Tryparsamide	750 to 900	400	1:2	1000 to 2500	300	1:3 to 1:8	0.620	3.0	1:12

* From data compiled by Moore (1933).
** I.M., Intramuscular injection.
† Calculation as follows: 0.4 ÷ 60 = 0.0067; 0.140 ÷ 0.0067 = 21 (see text).

Clinical Indices of Therapeutic Efficiency. Experimental data obtained from animals have limited applicability to man. Several examples will make this clear. The single dose method is employed to test the sterilizing effects of arsenicals in rats or mice infected with trypanosomes. Rabbit syphilis is readily cured by arsphenamines whereas human syphilis requires many months of continuous therapy. Again, animals do not show some of the severe types of reactions seen in human beings, including optic damage, toxic jaundice and exfoliative dermatitis. Finally, the therapeutic index of silver arsphenamine, for example, as indicated in Table 49 and calculated from data in rabbit syphilis, is greater than that for arsphenamine, but the clinical evidence strongly supports the view that in human syphilis the therapeutic index of arsphenamine and mapharsen is definitely superior to that of any other member of the group.

For these reasons, the clinical efficacy of the arsphenamines offers the only valid means of comparing the various drugs. Biological cure of syphilis would be the best measure but this cannot readily be judged. Ultimate clinical "cure" is more readily determined, but may require years of observation. The more immediate evidence of therapeutic efficiency of the arsphenamines is obtainable from a study of their ability to cause (1) the disappearance of surface spirochetes, (2) healing of visible lesions, and (3) reversal of the positive blood Wassermann reaction in early syphilis.

(1) The Disappearance of Organisms from Surface Lesions. Dark field examination reveals that adequate doses of any of the arsphenamines except bismarsen

cause disappearance of treponemes from moist lesions of early syphilis within 24 hours. Bismarsen requires three to six days for this result and tryparsamide has absolutely no treponemicidal effect. After full doses (0.3 to 0.4 gram) of arsphenamine itself, organisms disappear within four to six hours. As the dose is lowered, proportionately more time is required. For example, 0.3 gram of silver arsphenamine clears the lesion of organisms in five to seven hours but 0.1 gram takes 20 to 56 hours or may even fail to kill the treponemes. Similarly, small doses of arsphenamine (0.1 gram) or neoarsphenamine (0.2 to 0.45 gram) may not destroy surface organisms. To control infectiousness rapidly, therefore, full doses of the arsphenamines should be given at the outset. The order of decreasing efficacy in causing the disappearance of surface organisms is as follows: arsphenamine, silver arsphenamine, sulfarsphenamine, neoarsphenamine, and bismarsen.

(2) *Healing of Visible Lesions* (*Skin and Mucosa*). The arsphenamines in adequate dosage are all quite efficient in causing healing of cutaneous and mucosal lesions of early syphilis (primary or secondary) within two to three weeks. Bismarsen is least rapid and tryparsamide is almost totally ineffective. Arsphenamine itself is definitely superior to the other members of the group in early syphilis. Compared with neoarsphenamine, arsphenamine produces healing with only one-third the dosage (1.3 vs. 3.8 gram), one-half the number of injections (2.7 vs. 5.8) and two-thirds the number of days (14 vs. 23) (Cannon and Karelitz, 1931). According to Moore (1933), the order of decreasing potency of the arsenicals in this respect is as follows: arsphenamine, silver arsphenamine, sulfarsphenamine, neoarsphenamine, bismarsen.

(3) *The Effect on the Blood Wassermann in Early Syphilis.* By the end of the first course of arsphenamine injections in seropositive primary and secondary syphilis, an average of 75 per cent of patients will have a negative blood Wassermann. Eight weekly injections of arsphenamine are approximately as effective in this regard as ten of neoarsphenamine and the total dosage of the former chemical is only half as much as that of the latter. Data regarding the action of each arsphenamine on the blood serology are incomplete but those available suggest that arsphenamine, mapharsen, silver arsphenamine and bismarsen have approximately the same efficacy, and that neoarsphenamine is slightly less satisfactory (Moore and associates, 1936). The rate of serologic reversal produced by a drug in early syphilis, however, is the least important clinical index for the final evaluation of that drug.

The exact status of mapharsen in comparison with the arsphenamines with respect to the first two clinical indices discussed cannot yet be stated. All available evidence, however, suggests that mapharsen, in the doses used, is at least as efficient as neoarsphenamine, and probably the equivalent of arsphenamine itself.

THE CLINICAL TOXICOLOGY OF THE ARSENICALS USED IN SYPHILOTHERAPY

The untoward responses produced by the antisyphilitic arsenicals may be divided into local accidents and systemic reactions. Some of the latter partake of the general type of toxicity seen with inorganic arsenic. Others are peculiar to the arsphenamines and tryparsamide. Finally, some responses are conditioned by the disease itself, and are seen only in syphilotherapy. The classification to be followed in this section is that adopted by Moore (1933).

Local Accidents from the Arsphenamines. These may be divided into tissue reactions to extravasation of an arsphenamine, pain during injection, and thrombophlebitis.

(1) *Tissue Reaction to Extravasated Arsphenamine.* With the exception of sulfarsphenamine and bismarsen, the arsphenamines cause marked pain and necrosis if injected

into tissues. If more than a drop or two of solution leak out of the vein or needle, severe pain and marked swelling, redness, and disability occur. Sloughing may result and months may then be needed for healing which usually results in extensive scar tissue formation. Mapharsen is less damaging in this regard. Careful technic and cessation of the injection at the first complaint of pain will avoid this accident. The local injection of sodium thiosulfate solution has been tried but does not materially affect the course of the tissue reaction. Aspiration if possible, infiltration with isotonic sodium chloride solution, rest of the part, hot applications and incision if fluctuation occurs are the measures to be used. Tryparsamide does not cause tissue irritation.

(*2*) *Pain in the Arm.* Pain during injection results from overalkalinized arsphenamine. Silver arsphenamine also causes pain at times but the reason is not clear. Mapharsen solution, if not injected rapidly, may produce local discomfort. The other agents are free of this property. Careful preparation of arsphenamine and dilution with salt solution rather than water aid in lessening pain.

(*3*) *Thrombophlebitis.* This occurs only after arsphenamine and is due to improper preparation of the solution. Use of the monosodium salt and saline solution for dilution rather than water may prevent this accident. Some patients readily develop thrombophlebitis which may occur after each injection. In order to save the veins for therapy, a shift to another arsenical is indicated, if indeed not imperative. Dislodging of the thrombus with resulting pulmonary embolism is exceedingly rare.

Systemic Reactions. These reactions are classified in a number of different ways, a circumstance which has resulted in confusion. The classification employed by Moore (modified from Kerl) is followed here.

The Jarisch-Herxheimer Reaction (*Therapeutic Shock*). This reaction, also known as therapeutic shock, occurs only to the first and not to subsequent injections of an arsphenamine. In much milder form, it may also occur after the first injection of an antisyphilitic heavy metal. The reaction is similar to that seen in tuberculous patients who are sensitive to a subcutaneous injection of tuberculin. Such a person reacts by showing a *local* response at the injection site, a *general* response of fever and malaise, and a *focal* response in the nature of a "flare-up" at the loci of tuberculous lesions in the body. The same type of reactions may be noted in the syphilitic patient receiving a first injection of an arsphenamine. The local response is absent because the intravenous route is used. The general response usually appears within a few hours after the drug is given and consists of a chill, rise in temperature reaching 103 to 104 F. and general malaise and aching. The focal responses occur wherever syphilitic lesions exist, and they are the feature of main concern.

In early syphilis, before secondary manifestations have appeared, the typical syphilitic rash may occur within one or two days after the arsenical. If cutaneous and mucosal lesions are already present, they are intensified. The patient with latent syphilis is not greatly disturbed except by a febrile episode. In late syphilis, however, marked responses may occur at the site of lesions. In three types of late syphilis, the Jarisch-Herxheimer reaction may cause serious if not fatal accidents. It may occur in cardiovascular syphilis, where the edema and swelling of the syphilitic involvement about the coronary ostia may result in sudden closure of a coronary artery, or where an aortic aneurysm may rupture; laryngeal syphilis, where a gumma may swell and cause death by asphyxia; cerebrovascular syphilis, where cerebral hemorrhage or thrombosis may result.

The Jarisch-Herxheimer reaction is thought to be due to the sudden death of a large number of treponemes caused by a large first dose of an arsphenamine with the consequent release of proteins and toxins from the parasites. Some believe the reaction is due to the sudden formation and local release in syphilitic foci of a large amount of toxic arsphenamine oxidation products formed by contact of the drug and the spirochetes.

The significance of the Jarisch-Herxheimer reaction, except for the special dangers already noted, is inconsequential. The patient may be warned concerning the possible appearance of a rash. Arsphenamine should not be used for initial treatment in late syphilis where the focal flare-up of certain lesions might be serious or even fatal. In such patients, it is better to initiate therapy prior to arsenicals with a heavy metal and iodides. Small doses of arsphenamine (0.1 gram) or neoarsphenamine (0.15 gram) are much less likely to cause therapeutic shock and therefore small amounts of arsphenamines are usually given in late syphilis to initiate arsenical therapy. The heavy metals and tryparsamide may rarely cause a mild Jarisch-Herxheimer reaction.

Acid Arsphenamine Reactions. The intravenous injection of 0.2 gram or more of unalkalinized acid arsphenamine almost always results in sudden death. The catastrophe usually results from mistaking arsphenamine for neoarsphenamine which requires no alkalinization. This error must be avoided by careful reading of the label and personal preparation of the drug by the physician. Death is caused by multiple minute pulmonary emboli due to intravascular precipitation of serum proteins and agglutination of red blood cells by acid arsphenamine. The patient may make no complaint and die without warning when he arises from the table. More usually, there is a sense of constriction in the chest, coughing, severe back pain, ashen pallor, fainting, shock and death in a few minutes. The appearance of any of these effects demands immediate cessation of the injection and verification of the solution. If the reaction is not fatal, treatment consists of absolute rest for a day or two, inhalation of oxygen, perhaps intravenous papaverine, shock therapy, etc.

Reactions Due to the Intravenous Route. Several reactions after the injection of antisyphilitic arsenicals are non-specific in character and are due to the use of the intravenous route.

(*1*) *Tubing Reaction.* This reaction is caused by failure properly to prepare new rubber tubing before using it in the gravity apparatus for arsphenamine injections. It most often consists of fever, vomiting and headache and can readily be avoided.

(*2*) *"Ether" Odor.* This odor occurs only after the intravenous use of arsphenamine, neoarsphenamine and mapharsen. The other antisyphilitic arsenicals do not cause this phenomenon. The odor, which is like that of ether or garlic, is due to the presence of the drug in the blood of the nasal mucosa and therefore occurs within a few seconds after the injection. Some patients become ill because of this odor or object to it so strenuously that another preparation must be selected. Holding the nose while breathing through the mouth, allowing a wintergreen or clove wafer to dissolve on the tongue, chewing flavored gum, or smelling perfume may lessen the patient's awareness of the odor.

(*3*) *Gastro-intestinal Reactions.* These may occur from any intravenous injection and comprise the most frequent type of reaction after the arsphenamines. Within four to 12 hours, symptoms of nausea, vomiting, diarrhea, headache and malaise develop and last a few hours, but occasionally may persist for several days. Women are more susceptible to this disturbance. Intramuscular injection may infrequently cause it and intravenous tryparsamide is rarely responsible. Arsphenamine is the chief offender (40 per cent of all injections), neoarsphenamine next (25 per cent) and then silver arsphenamine (15 to 20 per cent). Mapharsen probably ranks in this regard between the two last-mentioned drugs. Gastro-intestinal reactions can be decreased in frequency and severity in several ways. The water used in preparing the drug solutions should be freshly distilled and sterilized on the day of use. Arsphenamine should not be underalkalinized and must be injected slowly. It is important that the patient eat lightly on the day of injection and omit the meal following the injection. The prevention of constipation during the course of arsenical therapy also helps. In early syphilis, when adequate treatment is essential, every attempt must be made to prevent gastro-intestinal reactions from interfering with the patient's continuance of therapy. The dose may be readjusted or another preparation tried.

Angioneurotic Syndrome. The most common type of angioneurotic reaction seen after arsphenamines is the nitritoid crisis, so named because of its resemblance to symptoms resulting from amyl nitrite inhalation.

(*1*) *Nitritoid Crisis.* This reaction occurs during or immediately after the injection. The conjunctiva becomes suffused very early and therefore the eyes should be closely observed during the administration of the drug. The patient then complains of being hot and experiences oppression in the chest and palpitation. If the injection is not stopped, the skin becomes flushed, the patient coughs and vomits, severe back pain occurs and the blood pressure falls. The picture is that of rapidly developing shock. In addition, other angioneurotic phenomena may occasionally appear with or without the above syndrome. These consist of swelling of the face, lips, tongue or eyelids and rarely edema of the larynx. Generalized giant hives may appear. The patient experiences fear of impending death and the reaction may sometimes prove fatal. The symptoms disappear in from 20 minutes to one hour without residual effects and even without treatment.

This alarming reaction rarely occurs with the first injection of an arsphenamine. Unfortunately, once it does appear it is likely to recur with subsequent injections. The incidence is about 0.1 to 0.5 per cent of all injections of arsphenamine and neoarsphenamine, but is considerably lower with the other drugs, unknown after mapharsen, and quite rare after tryparsamide. Certain lots of drug are more prone than others to cause the crisis.

Etiology. The cause of the nitritoid reaction is disputed. Rapid injection is undoubtedly the major factor in most cases. The similarity to acid arsphenamine reactions has suggested that here also agglutinated red blood cells may form multiple emboli and account for many of the symptoms. It is also possible that a histamine-like substance is produced or that a toxic amount of an arsphenamine oxidation product of the drug is formed. A likely explanation is that the physicochemical properties, especially the colloidal nature, of the arsphenamines are responsible for the production of symptoms (Hirschfelder and Wright, 1930; Shivers, 1933).

Prevention. Prophylaxis of the syndrome depends upon *very slow injection* of the arsphenamine, a shift to another batch of drug or employment of an arsenical with a lower incidence of such reactions (silver arsphenamine or mapharsen). The patient should be observed closely during the injection which should be stopped at the very earliest appearance of conjunctival suffusion, flushing, coughing, etc. Epinephrine (if not contraindicated) may be given intramuscularly (0.5 cc) five minutes before the arsenical, or 50 mgm of ephedrine sulfate may be taken orally one hour before each treatment. Similarly, one mgm of atropine sulfate injected subcutaneously 20 minutes beforehand may prevent the reaction. In some cases, the administration of one-tenth of the dose of an arsphenamine followed by an interval of an hour before the remainder is injected will solve the difficulty, but this is cumbersome.

Treatment. Therapy demands the intramuscular injection of 0.5 to 1.0 cc of a 0.1 per cent epinephrine hydrochloride solution, which usually combats all symptoms effectively; slow intravenous administration of 0.2 cc of epinephrine solution may be necessary in cases with marked syncope. A sterile syringe filled with epinephrine solution should always be ready for such an emergency. Rest in bed is compulsory for several hours or more.

(2) *Shock-like Reactions.* Infrequently, a patient may develop severe shock immediately or several hours after the intravenous injection of an arsphenamine. The signs are those described under the shock syndrome. Epinephrine fails to effect improvement and the therapy should be that for shock. It has been suggested that acute injury to the adrenal glands by the drug may account for this serious accident.

Acute Heart Failure. This catastrophic accident may result when an arsphenamine is injected in a patient with myocardial damage from cardiovascular syphilis. Symptoms occur immediately and are almost always fatal. In most cases the etiology is the sudden onset of ventricular fibrillation. This can be prevented by avoiding arsenicals in the initial treatment of cardiovascular syphilis. Should recovery occur, further use of any arsphenamine is prohibited.

Arsphenamine Dermatitis. The arsphenamines can produce every known type of skin eruption. These can simulate many diseases, exanthems and drug rashes, and vary in character from mild erythema or urticaria to severe and often fatal exfoliative dermatitis. The distribution may be widespread, or localized as in the case of herpetiform and fixed arsenical lesions. The diagnosis of such eruptions and their differentiation from those not due to arsenic are often difficult problems which may puzzle even expert syphilologists.

Diagnosis. It is extremely important to determine if possible, whether the dermatitis is due to the arsphenamine. Certain forms of arsenical eruptions signify sensitization and intolerance to the drug. Continued medication may result in serious illness or death. If the lesions are not due to arsenic or are not associated with visceral damage (especially renal and hepatic injury and blood dyscrasia) or with evidence of permanent arsenical sensitization, arsphenamine may be continued without danger. If arsenic is unnecessarily withheld, the physician runs the risk of giving inadequate antisyphilitic therapy. When in doubt, he should call in expert advice, and if this is not available treatment should be stopped, especially if the eruption itches or is vesicular or scaling. "If the practitioner is confronted by a patient who develops in the midst of antisyphilitic treatment any skin eruption not readily recognizable as *not* related to arsphenamine, the safest course to pursue is to discontinue treatment at once" (Moore, 1933).

In patients without syphilis but with a non-syphilitic infection, the injection of an arsphenamine may be followed shortly by an erythematous eruption and an associated febrile episode which disappear within two or three days.

Prognosis Regarding Continuation of Arsphenamine. The major dermatitides seen with arsphenamine are due to drug sensitization and nearly always necessitate complete and permanent abandonment of arsenical treatment. The serious forms of dermatoses are the macular, maculopapular, papulovesicular, vesicular, exfoliative, lichenoid and purpuric. These lesions are expressions of permanent sensitization and often are accompanied by associated visceral damage. The exfoliative post-arsphenamine dermatitis is an extremely serious syndrome and the mortality rate is 25 per cent. Some patients with fixed exanthems and occasional cases of macular and maculopapular eruptions may receive arsphenamine again if great caution is employed.

Prevention. It is therefore important to look for early symptoms of cutaneous or mucosal involvement in every patient receiving antisyphilitic arsenicals. The patient should be questioned before each injection, particularly concerning itching, fever, malaise, transitory or mild eruptions, and his body surface should be carefully examined. Despite every precaution, however, a severe or fatal exfoliative process may occur suddenly.

Incidence. Sulfarsphenamine is the worst offender in causing major dermatoses and the incidence is several times higher than with other drugs of the series. Arsphenamine, neoarsphenamine and silver arsphenamine are offenders in this order of decreasing frequency, but some experts report that the incidence for neoarsphenamine may be as high as, if not higher than, that for arsphenamine. About one patient in every 150 receiving either arsphenamine or neoarsphenamine develops post-arsphenamine dermatitis. The eruption tends to appear during the first dozen or so injections, that is, in the first or second course of an arsphenamine. Rarely, exfoliative dermatitis may appear after the first injection. The many other contributory factors involved may be found in the excellent discussion of this subject by Moore (1933).

The arsenical sensitization responsible for this form of dermatitis lasts for many years. It has been shown that minute amounts of arsphenamine given years later may induce another attack. In one case, 0.005 mgm (!) of arsphenamine, given intradermally to a sensitive patient who had a severe dermatitis six years previously, caused the eruption to reappear. The sensitization usually extends to the entire arsphenamine group but not to inorganic or pentavalent arsenicals. Passive transfer tests for this drug sensitization fail and desensitization is impossible.

Testing of Tolerance. Various types of skin tests designed to demonstrate drug allergy (scratch, intradermal, patch) are of no great practical value in detecting arsphenamine sensitivity. Patients known to be sensitive may not react at all, and normal persons may show positive responses. The tests are therefore nonspecific and may be dangerous either by provoking a serious reaction or by sensitizing an individual who must later receive an arsphenamine. Robinson (1934) has concluded from his studies on the patch test that it may offer confirmatory evidence in a patient known to be sensitive to arsphenamines, but the test cannot be used to demonstrate arsphenamine sensitization or to predict the desirability of continuance or interruption of therapy in patients who have had post-arsphenamine dermatitis.

When it is urgent to determine whether arsphenamine may again be used, a small amount of the drug may be injected intravenously several months after the dermatitis has subsided. This is justified only if it is uncertain whether the original dermatitis was due to arsphenamine sensitization. A different arsphenamine should be selected and the first dose must not be over 25 mgm. Itching or rash suggests that sensitization is present. Undue malaise or fever may signify the same, especially if there is leukopenia with a decrease in neutrophils and an elevation of monocytes or especially eosinophils. Under these circumstances arsphenamine therapy must be permanently abandoned and the patient warned that subsequent injection of an arsphenamine may prove fatal. If no untoward effect occurs from the first injection, it may be repeated cautiously each week and the amount of drug increased by small amounts (25 to 50 mgm per dose) until full doses are again tolerated. It should be repeated that this resumption of arsphenamine therapy is justified only if the nature of the original rash is in doubt. If the eruption itched intensely, contained vesicles, scaled or exfoliated, the eruption was due to arsphenamine therapy and further use of the group is barred.

Treatment. The major arsphenamine dermatoses require hospitalization, complete rest and expectant treatment. Sterile sheets and dressings, colloidal baths (require painstaking technic) and olive oil rubs minimize infection and decrease itching. The value of sodium thiosulfate has been questioned and remains a problem. The theories advanced for its use in arsenical and heavy metal poisoning are conjectural (page 743). Moore (1933), after seven years of patient trial, saw no evidence that thiosulfate was of value and abandoned it. The drug is fairly non-toxic and if one decides to use it the dose is 1.0 to 2.0 grams given daily intravenously in five to 10 cc of water. Calcium has been recommended in the therapy of the major forms of dermatitis on the assumption that this cation alters capillary permeability and relieves the symptoms of liver damage. Clinical results from its use are difficult to appraise. The gluconate of calcium in a dose of 10 cc of a 10 per cent solution may be injected intravenously each day.

Argyria. This rare reaction is usually mild and occurs in patients receiving silver arsphenamine in conjunction with bismuth injections. The description and mechanism of argyria are presented elsewhere. The buccal pigmentation is indistinguishable from that caused by bismuth alone. A minimum of six to eight grams of silver arsphenamine (20 to 25 injections) must be administered before early silver pigmentation appears in the skin. This pigmentation remains mild and does not deepen unless both silver arsphenamine and bismuth medication are continued. The possibility of argyria need be considered only when prolonged treatment with silver and bismuth is contemplated.

Nervous System Reactions. (*1*) *Neurorecurrence.* This reaction has been termed the "bugbear of early syphilis." It is not due to a direct action of the arsenicals, as once believed, but to their improper use. The neurorecurrence is caused by inadequate therapy and occurs about eight weeks (one to nine months) after the cessation of arsenical treatment in early syphilis. The incidence is only two per cent of poorly treated patients, but the symptoms are severe. These are varied but often take the form of an acute syphilitic meningitis, cranial nerve palsy, hemiplegia, etc. The prognosis is good so far as survival is concerned but poor in regard to functional recovery. The cause of the neurorecurrence is probably that incomplete therapy with arsenicals allows some spirochetes to survive but prevents immune processes from keeping pace. When therapy is stopped, the organisms grow rapidly without hindrance and cause fulminating nervous system disease. The phenomenon of neurorecurrence emphasizes the necessity for continuous intensive arsenical treatment in early syphilis. Patients should be warned of the dangers of interruption of therapy. Neurorecurrences are treated by intensive arsenical medication.

(*2*) *Polyneuritis.* This infrequent reaction is most often caused by sulfarsphenamine, occasionally by neoarsphenamine. Polyneuritis does not occur until 20 or more arsphenamine injections have been made. It is usually mild and disappears quickly after arsenic is discontinued. Further use of the drug may cause extensive nerve damage with slow and incomplete recovery. The rare possibility exists that syphilis or bismuth is the cause of the polyneuritis. Treatment does not differ from that for other forms of multiple neuritis.

(*3*) *Hemorrhagic Encephalitis.* This serious reaction is rare in the United States. It occurs after the first three or four arsenical injections and is characterized by severe headache, high fever, convulsions and coma. The severe forms are usually fatal. The brain shows edema ("serous apoplexy") and multiple punctate hemorrhages. The cause is unknown. Treatment consists of spinal drainage and symptomatic measures.

Reactions of the Bone Marrow. Blood dyscrasias due to the arsphenamines are extremely serious but rare. The incidence following sulfarsphenamine is higher than after the other drugs, and neoarsphenamine is the second greatest offender. Tryparsamide has not been known to injure hemopoietic tissue. All elements of the bone marrow may be depressed to cause aplastic anemia, or the platelets and white cell precursors may be injured selectively. Symptoms occur late in the course of treatment. The occurrence of blood dyscrasia following an antisyphilitic arsenical bars permanently the resumption of therapy with any arsphenamine. Even tryparsamide should not be employed, unless by an expert.

(*1*) *Thrombocytopenia.* This is probably due especially to depression of formation of platelets, but neoarsphenamine, in particular, appears capable of exerting a harmful effect upon thrombocytes in the circulation. The syndrome is characterized by all the laboratory and clinical features of symptomatic purpura. Hemorrhages into the skin and mucosa may occur soon after injection, or after several days. The purpura lasts two or three days and recedes. Recovery is the rule. The risk to life is small and though transfusion may be indicated, untreated patients usually recover readily.

(*2*) *Agranulocytosis.* This is due to selective depression of the bone marrow precursors of granulocytes. The onset is sudden and occurs from several hours to two weeks after injection of the arsphenamines. Soreness of the throat or gums during arsenical therapy calls for white blood cell and differential counts. The laboratory and clinical features are those of other forms of malignant neutropenia, such as that occurring after aminopyrine. The treatment is similar to that outlined elsewhere. In some cases, the number of both granulocytes and platelets may be simultaneously decreased.

(*3*) *Aplastic Anemia.* This is a highly fatal syndrome which accounts for more than one-half of the bone marrow dyscrasias caused by the arsphenamines. Symptoms may appear a day or two after injection or may be delayed for a month. The clinical and hematological picture does not differ from that of aplastic anemias caused by other agents. All elements of the bone marrow are depressed. In addition to anemia, there are granulopenic and hemorrhagic phenomena. The course is downhill and death occurs in approximately 80 per cent of the cases. The only known treatment consists of repeated blood transfusions and the use of the granulopoietic agents employed in malignant neutropenia.

Jaundice Following Arsphenamines. Jaundice occurring during antisyphilitic arsenical therapy is not always due to the drug, but may be due to any of the usual causes as well as to syphilis itself. In a detailed study of 158 cases of jaundice occurring among 18,250 patients receiving antisyphilitic therapy at the syphilis clinic of the Johns Hopkins Hospital from 1919 to 1934 inclusive, Soffer (1937) reported the incidence of postarsphenamine jaundice following the various antisyphilitic arsenicals as follows (the figures in parentheses representing the total number of cases treated): arsphenamine, 1:102 patients (10,755); neoarsphenamine, 1:157 patients (6445); tryparsamide, 1:450 patients (2700); silver arsphenamine, 1:356 patients (1425). The incidence of arsenical jaundice after arsphenamine and neoarsphenamine in the United States may be taken as approximately one case in 125 patients or one in 1000 injections. More rarely, tryparsamide and mapharsen may cause jaundice. The icterus may appear during therapy or months after the last injection, and there is no relation between it and the total amount of drug used or the stage of syphilis. Liver injury may be mild or so severe that acute yellow atrophy and death ensue. Pregnancy apparently predisposes to the more severe grades of hepatitis. The incidence of postarsphenamine jaundice is three times as high in white patients as in colored persons. The laboratory and clinical picture does not differ from that of other cases of jaundice of hepatic origin.

Some evidence of slight impairment of liver function is detectable by dye tests and serum bilirubin determinations in about 25 per cent of patients undergoing therapy with arsphenamine, but jaundice remains latent. The cause of postarsphenamine icterus is unknown but it may be due to one or a combination of the following factors—the drug, syphilis itself, or intercurrent infection. The evidence is convincing that many cases represent attacks of non-specific catarrhal jaundice occurring in patients whose livers are subjected to the added insults of syphilis and an arsenical.

When the jaundice is due to the antisyphilitic arsenical, it is usually hepatogenous in character, that is, due to injury to the liver parenchyma. However, in some cases, postarsphenamine jaundice may be obstructive in character and the clinical picture may so closely resemble occlusion of the common bile duct that patients have been subjected to exploratory operations. Hanger and Gutman (1940) have reported 12 cases of the obstructive type, the principal lesions being pericholangitis and bile thrombi in the finer biliary radicles. Individuals with this form of postarsphenamine icterus eventually recover, and treatment should be directed toward promoting drainage of the biliary tract (page 796) rather than toward the conservation of liver parenchyma, which remains essentially uninjured.

Treatment of the usual case of postarsphenamine jaundice differs in no wise from that for hepatogenous jaundice and liver damage from other causes. The outlook for complete recovery is excellent, but in pregnant patients grave icterus may develop and lead to fatal hepatic atrophy. During the episode of jaundice, no arsphenamine is given. Therapy is carried along with iodides and bismuth in patients who have early syphilis. Two or three months after the jaundice has faded, arsphenamine may be resumed but small doses (0.05 gram) are used at first. The dose is then increased by small weekly increments. No recrudescence of hepatic symptoms occurs in the majority of cases, but patients who have had post-arsenical icterus may show impaired liver function for many years.

Renal Damage. Renal injury from antisyphilitic arsenicals is rare. Cautious treatment with neoarsphenamine of patients with pre-existing non-syphilitic nephritis does not appear further to damage the kidneys. Sulfarsphenamine may occasionally cause serious hemorrhagic nephritis. The same syndrome may also occur associated with dermatitis or blood dyscrasia caused by an arsphenamine.

Tryparsamide Toxicity. Tryparsamide does not cause the serious reactions produced by the arsphenamines. The chief danger attending its use is *visual injury.* The incidence is rather high and Woods and Moore (1924) reported it to be more than 15 per cent; but Sloan and Woods (1936), in a review of the literature, record 71 objective reactions (3.4 per cent) in a total of 2087 patients receiving tryparsamide. Almost 10 per cent of patients receiving tryparsamide experience subjective visual changes consisting of "shimmering" or "dazzling" lasting for days to weeks. In about one-third of these cases objective evidence of concentric contraction of the form fields is discoverable. This may progress to blindness if the drug is not discontinued. In some cases, blindness may occur suddenly, especially if there is pre-existing optic injury. Optic atrophy, therefore, usually contraindicates the use of tryparsamide. If untoward effects are not experienced within the period of the first 12 tryparsamide injections, they are likely never to occur. All persons who are to receive the drug should have preliminary visual field and acuity tests. In patients with normal vision and optic fields, it is safe to employ the drug provided medication is terminated as soon as any visual defect appears. The patient should be warned to report the earliest symptoms of visual disturbance. Impairment of central vision or contraction of the visual field calls for immediate and permanent cessation of tryparsamide therapy. Central visual acuity fortunately returns but peripheral impairment persists. The literature on the toxicity of tryparsamide is discussed in detail in the review by Hinrichsen (1939).

Tryparsamide can also cause jaundice, which is usually mild. That the drug is not as innocuous to the liver as was formerly believed is indicated by the report of Traenkle and Dolce (1939) who record two fatal cases of liver atrophy due to tryparsamide. Untoward reactions to the drug appear to be on the increase, and include various forms of dermatitis, gastro-intestinal disturbances and nitritoid and allergic responses (Kopp and Solomon, 1940; Hinrichsen, 1939).

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CHAPTER 54

DRUGS USED IN THE CHEMOTHERAPY OF SYPHILIS

II. BISMUTH, MERCURY AND IODIDES

BISMUTH AS AN ANTISYPHILITIC

Historical. Although bismuth was first tried in human syphilis in 1889, it was not until many years later that the value of this metal was established by careful laboratory investigation. In 1916, Robert and Sauton studied the effect of bismuth in rat trypanosomiasis and fowl spirillosis, and in 1918 Kolle and Ritz demonstrated promising results from the drug in syphilitic rabbits. Sazerac and Levaditi (1921, *et seq.*) and Fournier and Guenot (1922) then introduced the drug in the modern therapy of human syphilis.

The antisyphilitic use of bismuth spread quickly and it rapidly displaced mercury as the heavy metal of choice. Bismuth is more effective than mercury but less so than the arsenicals. Its chief value is in conjunction with arsenicals; but, in some patients, it may of necessity become the mainstay of syphilotherapy.

Mechanism of Antispirochetal Action. Bismuth is poorly effective in trypanosomal diseases and therefore most of the experimental work on its mode of action has been confined to rabbit syphilis. The rapid and apparently complete cure of rabbit syphilis, as indicated by the disappearance of organisms and the lack of infectiousness of transferred lymph nodes, suggested that bismuth was a potent and direct treponemicide. Furthermore, a variety of bismuth preparations accomplished this curative effect and the margin of safety was excellent (one to 50).

Human syphilis, however, is considerably different from the disease in rabbits and it soon became clear that the experimental evidence was not directly translatable to clinical therapy. It was found, for example, that treponemes did not disappear from surface lesions of man for days or weeks after bismuth therapy was instituted. This was in sharp contrast to the arsphenamines which were effective within a few hours. Evidently the alleged directly spirocheticidal action of bismuth in rabbits required reinvestigation.

Kolle and Evers (1926) injected the insoluble compound, bismuth oxychloride, into the ears or thighs of rabbits to create a bismuth depot. The animals were subsequently inoculated intratesticularly with treponemes. Control rabbits similarly inoculated acquired chancres but the bismuth-injected rabbits did not. Apparently they were protected by the low bismuth concentration maintained in their tissues by the drug depot. Upon surgical removal of this depot, scrotal chancres appeared in the bismuth-treated animals, thus indicating that the treponemes were alive and pathogenic but had been held dormant by the metal. Kolle and Evers therefore concluded that bismuth was treponemistatic and not treponemicidal.

Levaditi and coworkers (1934) repeated these ingenious experiments, but used a liposoluble salt of bismuth instead of the oxychloride. Under these circumstances, the rabbits were completely protected from spirochetal infection both before and after the surgical removal of the bismuth depots. Therefore it must be concluded that, in rabbit syphilis at least, bismuth is capable of a treponemicidal and sterilizing action.

It is not clear, however, whether bismuth as used in human syphilis actually destroys spirochetes. It has been shown that healed syphilomas in rabbits contain infinitesimal amounts of bismuth (two to eight micrograms per gram of dry substance) despite the fact that non-syphilitic tissues of the body may attain much higher concentrations of the metal (Levaditi and Manin, 1934). This suggests that minute amounts of bismuth are capable of treponemicidal action, and Levaditi has expressed the opinion that bismuth may act as a catalyst for some unspecified lytic system.

Earlier *in vitro* work appeared to indicate, however, that bismuth, like arsphenamine, failed to show marked parasiticidal effect. It was claimed that incubation with tissue extract rich in glutathione apparently transformed a bismuth salt into a new and highly treponemicidal substance. To this newly formed but hypothetical compound was given the name "bismoxyl" (Levaditi and coworkers, 1923; 1924). No such body of evidence existed concerning the nature of this substance as had accumulated for "arsenoxide," the parasiticidal oxidation product of the arsphenamines. This work appeared to signify that the antisyphilitic action of bismuth is mediated through a conversion product formed by the tissues of the host.

Bismuth has also been viewed as a "resistance-builder," that is, an agent which increases the body's immunity to syphilis. Moore (1933) concludes, however, that this assumption does not fit the observed facts. Rather, bismuth appears to prevent the spread and multiplication of the treponemes and to depress the disease to the point where the degree of resistance already present in the body can control the infection. Although a final statement regarding the mechanism of bismuth action is not possible, the facts at hand suggest that the metal is markedly treponemistatic and moderately treponemicidal. As used clinically in human syphilis, bismuth cannot compare with the arsenicals in the ability to kill spirochetes.

Eagle (1938, 1939) has reinvestigated the *in vitro* antispirochetal potency of numerous bismuth preparations with illuminating results. Using pathogenic *Spirocheta pallida* (Nichols strain as well as strains freshly isolated from human cases of syphilis and tested after one or two passages through rabbits) and six water-soluble commercial preparations of bismuth, Eagle found that the metal immobilized the spirochetes, rendered them non-infectious for rabbits, and presumably killed them. Compared on a molar basis, the bismuth compounds were ¼ to $\frac{1}{28}$ as active as arsenoxide (mapharsen). When tested in the presence of the edematous ooze from a rabbit chancre, a fluid presumably corresponding to the extracellular fluid at the inflammatory focus, the minimal effective antispirochetal concentrations of two water-soluble bismuth preparations satisfactorily correlated with those of arsenoxide and the arsphenamines in relation to the therapeutic doses of bismuth and arsenic and the concentrations probably obtained clinically in tissue fluid. There was no indication that tissue derivatives in any way contributed to the *in vitro* antispirochetal activity of bismuth. Indeed, as in the case of the arsphenamines, the addition of tissue extractives regularly and markedly inhibited this activity, at times reducing it eighty-fold. Eagle concludes that bismuth acts neither as a catalyst, inhibitor nor precursor substance, but acts directly on the parasites as is also true of arsenoxide. Molecular oxygen is not needed for this treponemicidal action of bismuth, and sulfhydril compounds definitely depress the potency of the metal (Eagle, 1939). For example, cysteine, glutathione, thioglycollic acid and presumably any compound containing a reactive SH group, added in large excess to a spirochetal suspension containing arsphenamines, arsenoxide, mercury or bismuth, almost completely abolished the antispirochetal action of the drugs. The results are consistent with the hypothesis that the antisyphilitic chemicals owe their therapeutic activity to their ability to combine with SH groups in the spirochete.

Clinical Status of Bismuth. In early syphilis in man, bismuth alone is quite superior to mercury, but is distinctly slower in action than the arsphenamines. The surface organisms disappear only after several days rather than hours, and thus infectiousness cannot readily be controlled by bismuth. Visible lesions heal only after weeks rather than days, and the Wasssermann reaction also becomes negative more slowly. The limited data available also indicate that infectious clinical relapse and serological relapse are common. For these reasons, the arsenicals remain the mainstay of therapy in early syphilis.

Bismuth is less toxic than mercury. When used in early syphilis in conjunction with arsenicals, bismuth is superior to mercury in respect to percentage of Wassermann reversals and incidence of infectious relapses. For example, if bismuth is substituted for mercury, the relapse rate falls from 9.8 per cent to 3.6 per cent. Bismuth is used as a valuable adjuvant in the intervals between courses of arsphenamine. It is employed alone only in certain patients who cannot be given arsphenamines because of poor health as, for example, in cardiovascular syphilis, or when serious toxic reactions occur to arsenic. Bismuth is so superior to mercury that the latter metal is prescribed only when convenience or cost demands its use.

Preparations. The number of bismuth preparations which the practitioner can employ in syphilotherapy is unfortunately so large that the situation is confusing. The available drugs will first be classified and described and in a following section the criteria for their selection will be given. The rigid control of toxicity and supervision of therapeutic potency observed for the arsphenamines are entirely lacking in the field of bismuth preparations. Fortunately, the Council on Pharmacy and Chemistry has introduced some order into the confusion. The physician, unless particularly well versed in this field, will do well to confine his selection to two or three of the bismuth compounds included in the N.N.R. (Table 50) or sanctioned by the Cooperative Clinical Group.

Bismuth compounds are best classified according to their solubility rather than their route of administration, because intramuscular injection is the preferred method of giving the metal. Intravenous injection is not permissible due to the high toxicity of bismuth by this route. The therapeutic index of bismuth administered intravenously is rarely more than 1:3. The oral administration of bismuth has received a limited but promising clinical trial and one preparation for oral use is accepted in N.N.R. (Table 50).

Commercial antisyphilitic bismuth preparations are either (1) soluble in water, or water-miscible solvents such as propylene glycol; (2) soluble in oil; (3) insoluble, and suspended in water; (4) insoluble, and suspended in oil.

Most bismuth compounds contain bismuth as the cation (electropositive form), but two preparations contain the metal as the anion (electronegative bismuth). One of these is *iodobismitol* and the second is a newly introduced compound, *sobisminol* ($NaBiO_3$ in propylene glycol and triisopropanolamine). The latter bismuth preparation has been studied especially by Hanzlik and his coworkers (1937, 1938) and also by Sollmann, Cole and associates, (1938) for both intramuscular and oral administration, and has been accepted by the Council (1939) for inclusion in N.N.R. (*See* also Meininger and Barnett, 1939; Scholtz and coworkers, 1939.)

In Table 50 are listed the Council-accepted bismuth preparations, their single doses and major characteristics. Details of these products may be found in the N.N.R.

The only official bismuth preparations used in syphilotherapy are *Bismuth Salicylate* (*Bismuth Subsalicylate*), U.S.P., B.P., *Bismuth and Potassium Tartrate* (*Potassium Bismuthyl Tartrate*), U.S.P., *Bismuth and Sodium Tartrate* (*Sodium Bismuthyl Tartrate*), B.P. and *Injection of Bismuth* (precipitated bismuth in glucose solution), B.P.

Dosage. The single dose for each preparation is given in Table 50. The rapidly absorbed and excreted compounds (iodobismitol, thiobismol, water-soluble tartrates) must be given two or three times weekly to insure adequate tissue and serum concentrations. The liposoluble and insoluble bismuth suspensions are given once weekly. A course of bismuth extends from six to 10 weeks, and in early syphilis such therapy is alternated with courses of arsenicals for a period of a year or more.

TABLE 50

BISMUTH PRODUCTS ACCEPTED FOR SYPHILOTHERAPY BY THE COUNCIL ON PHARMACY AND CHEMISTRY FOR INCLUSION IN NEW AND NONOFFICIAL REMEDIES

CLASSIFICATION	TRADE NAME	CHEMICAL NAME, VEHICLE OF SUSPENSION OR SOLUTION, AND CONCENTRATION	APPROXIMATE CONTENT OF METALLIC BISMUTH IN MGM PER CC OF DRUG SOLUTION	RECOMMENDED INTRAMUSCULAR DOSE
Insoluble, used in oil	Bismuth Subsalicylate *	10% suspension of basic bismuth salicylate in peanut oil. Each cc contains 0.1 Gm. of drug.	57	2 cc (0.2 Gm.) weekly
	Oleo-Bismuth	Bismuth oleate, suspended in olive oil. Each cc contains approximately 0.25 Gm. of drug.	50	2 cc (0.5 Gm.) once or twice weekly.
	Tartro-Quiniobine	Suspension of quinine bismuth iodide 0.072 Gm. and sodium potassium bismuthyl tartrate, 0.032 Gm. in 1 cc of olive oil.	25	1 to 2 cc weekly
	Mesurol	Basic bismuth methoxy hydroxy benzoate, 20% suspension in sesame oil. Each cc contains 0.2 Gm. of drug.	110	1 cc (0.2 Gm.) weekly
	Potassium Bismuth Tartrate *	10% suspension of basic bismuth potassium bismuthotartrate in peanut oil with 0.4% butyn. Each cc contains 0.1 Gm. of drug.	66	2 cc (0.2 Gm.) weekly
Soluble, used in oil	Bismo-Cymol	Basic bismuth salt of camphocarboxylic acid, in olive oil. Each cc contains 0.125 Gm. of drug.	50	2 cc (0.25 Gm.) two times weekly
	Quiniobine	Quinine bismuth iodide rendered soluble in olive oil by means of lecithin. Each cc contains 0.158 Gm. of drug.	30	1 to 2 cc (0.16 to 0.32 Gm.) two times weekly
Soluble, used in aqueous medium	Bismosol	Potassium sodium bismuthotartrate in 10% glucose solution, 0.1 Gm. in 1 cc.	35	1 cc (0.1 Gm.) two or three times weekly
	Bismuth Sodium Tartrate	0.3 Gm. drug and 0.04 Gm. benzyl alcohol in 2 cc of a 25% sucrose solution.	11	2 cc (0.03 Gm.) two or three times weekly
	Thio-Bismol	Sodium bismuth thioglycollate, 0.2 Gm. to be dissolved in 1 cc of distilled water.	76	1 cc (0.2 Gm.) two or three times weekly
Soluble in propylene glycol	Iodobismitol with Saligenin	Sodium iodobismuthite (sodium bismuth iodide) and sodium iodide dissolved in propylene glycol. Each cc contains 60 mgm of the bismuth salt.	13	2 cc (0.12 Gm.) two to three times weekly
	Sobisminol Solution	Interaction product of sodium bismuthate, triisopropanolamine and propylene glycol. Each cc contains 20 mgm of bismuth.	20	1 cc to 2 cc twice weekly
Bismuth for Oral Use	Sobisminol Mass	Interaction product of sodium bismuthate, triisopropanolamine and propylene glycol.	Each capsule contains 150 mgm of metallic Bi.	2 to 3 capsules three times daily

* Other vehicles or concentrations are available.

Selection of Preparations. *The chemotherapeutic index* of bismuth-containing drugs does not enter as a factor in the physician's selection of antisyphilitic remedies because, given intramuscularly, all the preparations have a high index. The margin of safety is often higher than for the arsphenamines and is considerably above that for mercury.

It has been claimed that certain bismuth preparations allow higher *effective tissue concentrations* of the metal than others and should therefore receive preference. Thus, for example, sodium iodobismuthite (iodobismitol) contains bismuth as the anion ($NaBiI_5$) and it is thought that this confers a special ability on the compound to penetrate the central nervous system (Hanzlik and associates, 1932, 1938). This claim has been denied by Klauder and Brown (1934), and by Levaditi and coworkers (1933) who found that liposoluble and other bismuth compounds containing bismuth as the cation allowed the same concentration in the nervous system as did sodium iodobismuthite. Indeed, Johnson and Barnett (1936) showed that iodobismitol did not decrease the incidence of positive spinal fluids when used instead of other bismuth compounds in conjunction with the arsphenamines in early syphilis. That iodobismitol, however, is a satisfactory bismuth preparation if given two or three times weekly has been shown by the extensive clinical study of Barnett and Kulchar (1937). Some workers believe that the iodine in the compound may improve the efficacy of the heavy metal.

It appears that far too little is known of the action of bismuth to assume that a higher tissue concentration at a particular site is directly correlated with antisyphilitic potency. In the case of the arsphenamines, it was shown that the arsenic content of the brain and spinal fluid was not directly related to the curative effects noted in central nervous system syphilis. The distribution and excretion of various bismuth compounds vary so considerably, and the relation of tissue concentration to antitreponemal action is so poorly understood that the practitioner must base his selection purely upon clinical results. Fortunately, there is a considerable body of clinical evidence to guide him in this respect.

The main decision is *whether to use a soluble or an insoluble bismuth compound.* The consensus of opinion is that bismuth depends for its beneficial effects upon the maintenance in the body of a low but effective concentration of the metal over long periods of time. Some believe that this is best done with preparations of *soluble bismuth.* It is claimed that these give a higher tissue concentration, and a more rapid excretion which insures against toxic cumulative effects. Injections of insoluble preparations are thought to supply an undependable and uncontrolled muscle depot of bismuth which yields an irregular and inadequate supply of the metal to the body, and constitutes a source of bismuth for potential poisoning. The theoretical arguments in favor of the soluble as against the insoluble bismuth preparations have been effectively presented by Hanzlik (1936).

Many expert syphilologists, however, advise the injection of *insoluble bismuth.* They claim that toxic effects are no more common after the insoluble than after the soluble preparations, and that the clinical results justify their use. Furthermore, they need be injected but once weekly which is a distinct advantage over the soluble drugs in regard to expense, comfort and convenience. The use of soluble compounds requires injection every second or third day because of their rapid absorption and excretion. Many patients either cannot or refuse to come for injections every other day. Moore (1933) sees no advantage either in the water or oil soluble compounds over insoluble bismuth, and prefers the latter (in the form of the salicylate) for general use. Tatum (1938) is definitely of the opinion, based on the results of his studies in experimental syphilis, that the best therapeutic indices are obtained with the relatively slowly absorbed bismuth compounds. He adds that "whereas rates of absorption of different bismuth compounds are different, bismuth on leaving the original depots settles down sooner or later to much the same form of ultimate complex regardless of how it was dressed up in the ampoule." Kolmer, Brown and Rule (1939) conducted a detailed experimental study in animals of the toxicity, absorption, excretion, and therapeutic effectiveness of the bismuth compounds commonly employed clinically in syphilotherapy. They concluded from their work that the majority of these compounds are acceptable in the treatment of syphilis provided that their dosage and frequency of administration are properly adjusted to maintain an adequate concentration of elemental bismuth in the blood and tissues over a period of time sufficiently long for the maximum therapeutic effectiveness consistent with lowest toxicity.

In *summary,* it may be said that where slow but comparatively constant and sustained bismuth action is desired ("consolidation" therapy), the oil suspensions of bismuth subsalicylate or sodium potassium bismuth tartrate should be injected once weekly. When more rapid bismuth action is wanted ("attack" therapy), as in patients who have late visceral syphilis and cannot be given arsenic initially, or who are sensitive to arsphenamines, the soluble products (thiobismol, iodobismitol, sobisminol, bismuth sodium tartrate) are given two or three times weekly (Cole, 1936; Cole and coworkers, 1939).

Certain insoluble bismuth compounds on the market cause more pain and local reactions than others, and various preparations of the same chemical may differ widely in these respects. In general, the salicylate is probably less troublesome than the tartrate, but the oil used in the suspension is also a factor. The technic of the intramuscular injection is extremely important in preventing serious accidents and in reducing pain and discomfort. This technic may be found in the package information of the bismuth drugs, in texts on syphilology, in the N.N.R., and in the governmental publications.

Routes of Administration. At present, the most valid route of administration of bismuth is deep *intramuscular injection* into the buttocks. The *intravenous injection* of bismuth is dangerous and has caused death. The therapeutic index of bismuth given by vein is only 1:3, whereas that of bismuth injected intramuscularly is, for most preparations, 1:50. Bismuth by *inunction* is worthless. Cutaneous absorption of bismuth, in sharp contrast to mercury, has not been demonstrated. The *oral administration* of bismuth has received some attention in late years. Most bismuth compounds are not absorbed sufficiently from the intestinal tract to allow the metal to reach an effective concentration in the tissues. Hanzlik and coworkers have reported on the oral use of bismuth in special solvents (sobisminol). This work is still in the developmental stage but the early reports are promising (Meininger and Barnett, 1939; Scholtz and coworkers, 1939). The oral use of sobisminol should be reserved for the present for use in patients unable to receive intramuscular therapy. The special indications, precautions, dangers and limitations of the use of bismuth by mouth in syphilotherapy have been outlined by the Council (1939).

Absorption, Distribution and Excretion. An enormous literature on this subject exists and it is neither possible nor desirable to present more than a summary of those facts which have bearing on the clinical use of bismuth in syphilis. The interested reader is referred for details to the reviews and publications of Lomholt (1928), von Oettingen (1930), Hanzlik and associates (1932, *et seq.*), Levaditi and associates (1933), Sollmann, Cole and coworkers (1933, 1937, 1938, 1939), and Kolmer, Brown and Rule (1939).

It is clear that the absorption and excretion of bismuth are important factors which determine the effective concentration and hence the antisyphilitic potency of bismuth in the tissues. Although considerable clinical information is available concerning the rates of absorption and excretion of the bismuth compounds used therapeutically, its significance is not entirely understood. The reason for this is that the data on human beings for tissue distribution of bismuth are meager, and there is no assurance that tissue concentration is an accurate index to the antitreponemal action of the metal.

Absorption. Intramuscular absorption of injected bismuth depends on a number of factors, including the nature, dose and tissue solubility of the drug, and the number and frequency of injections. The solubility of the drug is important in determining the spreading of the metal in the muscles. Oily solutions or suspensions do not spread and thus offer less absorbing surface. Bismuth is precipitated locally at the site of injection. This holds true even for the water-soluble bismuth preparations, for example, tartrates and citrates. Compounds which are both water and tissue-soluble (*e.g.,* thioglycollate) are absorbed rapidly and not precipitated locally. Precipitated bismuth is gradually changed to a tissue-soluble form and then absorbed. Phagocytes may play an important rôle in transporting bismuth particles from muscle depots, especially when insoluble suspensions are injected.

The *rate of absorption* from the muscle depot has been studied by x-ray, chemical and histological methods. The results obtained are in general agreement and correlate well with the added evidence obtained from the urinary excretion rates. The speed of absorption is most rapid for the aqueous or water-miscible solutions (citrates, tartrates, iodobismuthite, thioglycollate and bismuthate-soluble); next in order are the oil-soluble bismuth drugs (bismocymol, quiniobine and biliposol); then come the oil suspensions of water-soluble bismuth drugs (tartrates), and finally the most slowly absorbed preparations, the oil suspensions of the insoluble bismuth compounds (subsalicylate, oleate, and benzoate).

The water-soluble compounds may be completely absorbed from the muscle in a few hours to a day or two. In contrast, the oil suspension of insoluble compounds may require many days or weeks for absorption, and may in part undergo local encapsulation.

Distribution in the Tissues. Bismuth has been detected in all tissues and fluids of the body. The correlation between tissue distribution and clinical efficacy of various compounds has not been made. The special problem of penetration of the nervous system by bismuth has been discussed. Tissue retention of bismuth continues for weeks or months after the excretion curve has reached a low constant level. This fraction of retained bismuth is apparently of more toxicological than therapeutic importance. Sollmann, Cole and associates (1938) determined at autopsy the concentration and quantity of bismuth in the viscera of 22 patients who had received during life various clinical preparations of the metal. The concentration of the element seemed to be determined especially by the total dosage of the bismuth rather than by the type of drug used. Particularly high values were found in the kidney and liver. The viscera retained the metal with great tenacity and practically indefinitely after the discontinuation of the drug. It has also been determined that bismuth passes freely through the placenta to become distributed in the fetal tissues, including the bones. For example, Whitridge (1940) demonstrated that when bismuth was given intramuscularly to pregnant women, roentgenographic examination of the newborn showed transverse bands of increased density near the ends of the long bones.

Excretion. Bismuth is excreted mainly in the urine. A small amount (10 per cent) is eliminated through the large bowel. The rate of renal excretion serves as a fair index of tissue absorption of the metal, and to a large extent is determined by the rapidity of entrance of bismuth into the circulation from the muscular depot. More important is the fact that the urinary bismuth is a reflection of the active and diffusible serum and tissue bismuth, upon which clinical efficacy probably depends, for the urine level of bismuth is directly dependent on the blood concentration. The values for the latter vary considerably but are probably between 0.02 mgm and 0.05 mgm per cent for a patient on bismuth medication. Regardless of whether bismuth is treponemistatic or treponemicidal, it is obviously effective in very low concentrations.

The *rate of bismuth excretion* in the urine and feces has been studied in man after single and multiple doses of most of the preparations used clinically. These studies have been performed especially by Sollmann, Cole and collaborators (1933, 1937, 1938). In general, the excretory rate of the various clinical compounds takes the same order as that given above for rapidity of absorption. Thus, the greatest urinary excretion after a single dose of a water and tissue-soluble compound (*e.g.*, thioglycollate) or of bismuth in a water-miscible solvent (*e.g.*, sodium iodobismuthite in propylene glycol) occurs on the day of injection and falls off rapidly thereafter. At the opposite extreme, the peak urinary excretion of bismuth after injection of an oil suspension of an insoluble product (*e.g.*, subsalicylate) may not occur for five or more days. Furthermore, the excretion continues at a low level for many weeks, due to the remobilization of metal from deposits in the tissues and viscera.

One important feature which has become increasingly obvious from the extensive clinical investigations on bismuth elimination is the great individual variation from person to person. *A preparation which allows a more or less continuous daily urinary excretion of two to four or more mgm of the metal during the course of bismuth therapy is believed to be satisfactory* (Cole and associates, 1939).

Clinical Toxicology. When an acceptable bismuth compound is given properly by the intramuscular route, toxic effects are rarely noted. The fears of those who dislike giving a large number of injections of insoluble bismuth have not been substantiated. Moore has given patients as many as 100 injections of bismuth salicylate (20 grams) over a period of two to three years without the least evidence of bismuth poisoning. Death from bismuth is exceedingly rare and is usually due to accidental intravenous injection.

Local Reactions or Accidents. Pain. Pain after intramuscular injection of bismuth is often due to faulty technic. Injection of one cc of air into the muscle before withdrawing the needle and routine massage are two ways of decreasing greatly the discomfort attending intramuscular bismuth therapy. Some compounds cause more pain than others and the solvent often is a determining factor. Thus bismuth salicylate in olive oil is quite irritating, but suspended in peanut oil the drug is quite bland.

Sterile abscess is infrequent. The campho-carboxylate compound is probably a greater offender than others in this regard (Moore) and therefore is not recommended. The buttocks can usually tolerate from 50 to 100 injections.

Sclerosing myositis, such as occurs after mercury, is almost unknown from bismuth. The addition of a local anesthetic to the bismuth preparation is illogical because the objectionable discomfort and soreness develop long after the anesthesia has disappeared.

Embolism. This accident occurs when the bismuth is injected into a blood vessel instead of muscle. If a vein is entered, oil embolism of the lungs may occur and cause grave shock or even death. Again, severe and sometimes fatal bismuth intoxication rapidly ensues. Arterial embolism results in painful induration of the buttock with characteristic skin changes over the area and sometimes tissue necrosis and sloughing. The insertion of a large dry needle (19 gauge) before the syringe is attached and retraction on the plunger for several seconds to see whether blood can be aspirated are precautions usually sufficient to prevent such accidents.

Systemic Reactions. Pigmentation. This consists of a bluish pigmentation of the gum margins and buccal mucosa. The bismuth line on the gums, which appears after six or more injections, has not the serious import of a lead line. After two dozen injections, most patients show pigmentation of the soft palate and inner surfaces of the cheeks. The coloration is due to deposition of bismuth in fibrous tissue cells of the summits of mucosal papillae. In itself the pigmentation has no serious significance, but it may be objectionable cosmetically. It withstands all attempts at removal, and persists for years with only slight fading. The color is more pronounced when silver arsphenamine is used in conjunction with bismuth. Rarely, generalized permanent discoloration of the skin (bismuthia) resembling argyria may result from unduly prolonged use of the metal.

Stomatitis. Ulcerative stomatitis calls for immediate cessation of bismuth therapy. It is rarely seen when the dose of bismuth does not exceed the average, and when oral hygiene is good. Dental prophylaxis to insure oral hygiene is highly desirable but not always attainable.

Jaundice. Jaundice of an obstructive form with enlargement of the liver may occur in the course of bismuth therapy. Jaundice is rarely serious and usually does not preclude the further use of the metal. It is often extremely difficult to determine whether the symptoms are due to intercurrent catarrhal jaundice or to the coincident use of arsphenamines. Nomland and associates (1938) reported 32 cases of jaundice presumably due to bismuth, an incidence of only one case in over 2200 injections. This is an incidence of jaundice which is about 40 per cent of that for neoarsphenamine.

Nephritis. Bismuth possesses the propensity for causing kidney injury. The accumulation of the element at the site of excretion favors renal damage. Nevertheless, as the metal is used clinically, it rarely causes impairment of renal function or urinary evidence of parenchymatous damage. Even patients with preexisting nephritis are often tolerant of bismuth. It is wise, however, to examine the urine routinely during bismuth medication and, if albumin or casts appear, the drug should be discontinued temporarily. With regard to the kidneys, bismuth is quite innocuous when compared with mercury.

Dermatitis. Various types of skin eruptions have been reported after bismuth but these are rare. Oddly, the lesions often simulate pityriasis rosea. If severe dermatitis develops due to bismuth, the metal should be permanently discontinued.

Miscellaneous Reactions. Gastro-intestinal upsets may occasionally occur and infrequently bloody diarrhea has been reported following bismuth. *Peripheral neuritis* due to bismuth is another rare occurrence. *Jarisch-Herxheimer responses* can follow bismuth but necessarily are mild, because the metal is not highly treponemicidal. The reaction is usually confined to cutaneous manifestations in early syphilis. Occasionally, a patient is seen who reacts to each injection of bismuth with *malaise, fever, headache,* and *pains in the joints and bones* sufficiently severe to necessitate cessation of the drug.

MERCURY AS AN ANTISYPHILITIC

Historical. The use of mercury in syphilis dates from the late 1490's. Until the introduction of the arsphenamines, this metal occupied the forefront of antisyphilitic therapy. After the discovery of the value of bismuth, mercury fell into the background and today it is employed only for rare and special purposes or when factors of convenience and cost demand its substitution for bismuth. For the prophylaxis of syphilis, on the other hand, mercury still occupies an important position.

Mechanism of Treponemicidal Action. Although mercury is highly treponemicidal upon direct contact with parasites in the test tube, it loses this potency when injected into animals. In this latter respect, it differs markedly from bismuth and arsenic. Mercury has a low therapeutic index and doses which cure animals of syphilis approach the lethal. Mercury also differs from bismuth and arsenic in that it has no value in trypanosomal infections.

Clinical syphilis is only slowly affected by mercury. Healing is delayed and treponemes persist in the lesions for long periods. It is doubtful whether mercury ever *cured* a case of syphilis in the four and one-half centuries during which it has been employed.

The low antitreponemal efficacy of mercury *in vivo* makes it unlikely that beneficial effects from the drug are due to a direct parasiticidal action. The many hypotheses concerning mercury as an agent which increases the host's resistance are unsupported by acceptable evidence. The most likely explanation is that mercury, similar to bismuth, exerts a treponemistatic action which reduces the infection to the level where the body's own defenses can cope with it.

Value and Clinical Status. Mercury is inferior to bismuth as an adjuvant to the arsphenamines in syphilotherapy. When employed with the arsenicals, it allows a higher incidence of infectious relapses and a lower percentage of serological reversals than does bismuth. When employed alone, a practice no longer necessary or permissible, mercury fails to curb infectiousness or prevent the progress of the disease. Mercury is also more toxic than bismuth and has a much lower therapeutic index. If the arsenicals cannot be used for any reason, bismuth and not mercury must provide the mainstay of therapy. However, mercury is a permissible substitute for bismuth under special conditions in early syphilis (page 996). In certain forms of late syphilis, mercury is occasionally given intravenously but the availability of quickly absorbed soluble bismuth preparations makes this practice obsolete.

Absorption, Fate and Excretion. The details of the absorption, fate and excretion of mercury are given elsewhere (page 732). Much clinical research has been conducted regarding the various soluble and insoluble organic and inorganic mercury preparations used in syphilis (*see* especially the work of Sollmann and associates, 1935). Unfortunately, the immediate clinical value of these findings is decreased by the fact that mercury is almost never used in syphilotherapy. Rather the value of such investigations rests in the fact that it has emphasized the possibility of accumulation of mercury in the tissues and poisoning from the use of the metal.

Routes of Administration, Preparations and Doses. In the early days of mercury administration, *inhalation* of mercury vapor was employed. This is dangerous and now entirely obsolete. Rarely, for mild treatment in elderly or debilitated patients with late syphilis, mercury may be given *orally,* for example, in such form as the protoiodide (Yellow Mercurous Iodide, U.S.P.), 0.02 gram three times daily. This therapy is never to be employed in early syphilis.

Occasionally, *intravenous or intramuscular injection of soluble mercuric preparations* may be indicated. For this purpose, either the succinimide (U.S.P.), cyanide (N.N.R.), oxycyanide (N.N.R., B.P.) or benzoate (N.N.R.) may be used. The dose of any of these is 0.01 gram daily for not more than 20 days. Early toxic symptoms are not unusual. *Mercuric Succinimide,* U.S.P., is probably preferable, being less toxic and less irritant to veins. The special indication for the intravenous use of mercury is the institution of prompt therapy in patients with late syphilis of the central nervous system, heart or liver in whom arsenicals are initially contraindicated. Satisfactory soluble bismuth preparations which allow high blood and tissue concentrations of heavy metal to be quickly reached have superseded the use of this type of mercury therapy.

Intramuscular injections of insoluble mercury are not advisable or necessary.

Toxic effects are common, absorption is uncontrollable, and local pain and sclerosing myositis are frequent.

Inunction is the most valid route of administration of mercury. The preparation used is the U.S.P. *Strong Mercurial Ointment* (metallic mercury, about 50 per cent); but, if this proves too irritating to the skin, it may be diluted (one-quarter to one-half) with cold cream. The daily dose is four grams and it is more convenient if the dispenser supplies the proper individual doses in waxed paper. The patient must be given definite instructions concerning how, where and how often to rub the mercury on his skin. For this purpose it is best to give printed directions and to impress upon him the necessity for following each detail with care. These directions can be found in texts on syphilology or in the governmental publications referred to previously. Inunction should be stopped at once if the teeth begin to ache, if the gums swell, hurt or bleed easily and if diarrhea or headache occurs.

The rubbing of mercury into various cutaneous areas of the body in rotation continues nightly for several weeks (six to 10) in the intervals between courses of arsenicals. Mercury by inunction can be substituted for bismuth in early syphilis but this should not be done until the 30th week of therapy (Table 51). Mercury rubs are inexpensive and practically free of cumulative toxic effects if the patient is alert to early signs of overdosage. By stopping the mercury and taking a hot bath, quick relief is afforded. On the other hand, the treatment is messy, and requires time and intelligent cooperation. Yet it may be necessary for financial reasons, in travelling patients, or in others unable to make weekly visits to the physician for bismuth injections.

Clinical Toxicology. The toxic effects of mercury have been discussed in detail (page 733). The particular features which serve as indices of early intoxication in the clinical use of mercury are stomatitis, gastro-intestinal disturbances and renal irritation. Strict oral hygiene and dental prophylaxis are essential and the occurrence of sore gums, aching teeth and excessive salivation calls for cessation of mercury. Diarrhea and abdominal pain may occur after inunction but are more likely to result from mercury given orally. The metal is contraindicated in all persons with pre-existing renal damage and the urine must be examined regularly in any patient receiving mercury. Dermatitis is ordinarily due to too vigorous rubbing of the ointment or to a hairy skin, but very rarely the metal can cause serious cutaneous eruptions even after systemic administration.

Use of Mercury in the Prophylaxis of Syphilis

Despite its limited value in syphilotherapy, mercury occupies a most important position in the prophylaxis of the disease. The compound used is *Calomel Ointment* (Ointment of Mild Mercurous Chloride), N.F. The value of calomel was demonstrated early in this century by Metchnikoff and Roux and thoroughly proved by the experiences of the United States Army and Navy medical services during the war of 1914–1918. Used properly and within one hour after the beginning of the first exposure, mercury protects against infection in 99.7 per cent of cases.

The exact technic of chemical prophylaxis in the male and female must be sought in texts on syphilology or in public health publications. The mercury ointments used are as follows: U. S. Army, mercurous chloride, 30 per cent, benzoinated lard, 65 per cent, white wax, five per cent; U. S. Navy, mercurous chloride, 33 per cent, camphor, two per cent, phenol, three per cent, anhydrous lanolin, 39 per cent, benzoinated lard, 20 per cent and beeswax, three per cent. Prophylaxis also includes the intra-urethral injection of argyrol (10 per cent solution) or protargol (two per cent solution) and is a combined treatment against syphilis and gonorrhea. Prophylaxis in the female is much more difficult than in the male.

Should one accidentally prick his flesh with a needle contaminated with the virus of syphilis (as when taking blood of a syphilitic patient), the infected part should be opened widely and packed freely with calomel ointment. The blood Wassermann should then be checked to see whether infection has been avoided. Arsenicals must not be used until the diagnosis of syphilis has been unequivocally established (page 995).

IODIDES IN SYPHILOTHERAPY

The iodides were introduced into syphilotherapy in 1836 and have been employed since then on a purely empirical basis. For years, mercury and iodides were the only drugs effective against the disease. Some syphilologists believe the iodides can well be dispensed with in syphilis, but this is a difficult point to prove.

Mechanism of Action. The iodides do not kill treponemes, and apparently have no direct action on the infecting organism. Effects similar to those seen after iodides in syphilis are noted in other *granulomatous lesions* such as *leprosy, sporotrichosis, blastomycosis* and *actinomycosis.* The iodides thus have some indirect action on syphilitic lesions but the nature of this remains obscure. It is thought that iodides may improve the effects of arsenicals and heavy metals, perhaps by aiding their penetration into syphilitic tissue. How the halogen does this is not clear. The usual statement that granulomatous tissues or pathological fluids contain more iodide than normal tissues and fluids needs correction. Again, iodides heal certain lesions of late syphilis even without the intervention of other drugs. The suggestion has been advanced that this is accomplished through an inhibition by iodides of an antiferment, thus allowing proteolytic enzymes to dissolve necrotic tissue; but this theory requires proof.

Clinical Status and Value. In *early syphilis,* iodides are not needed either for control of infectiousness, healing of lesions, prevention of relapse or reversal of the serology. All these features are accomplished by the use of arsphenamines alternated with courses of bismuth. Some clinicians, however, employ the iodides during the courses of heavy metals in early syphilis on the basis that they "do no harm and may do good."

In *late syphilis,* however, the impression remains strong that lesions heal and pain disappears more rapidly when iodides are used in conjunction with arsenic or heavy metals than when the halogen is omitted. The iodides are particularly valuable in late gummatous lesions of any type, in syphilis of the skin, bones or liver, in cardiovascular syphilis and in acute syphilitic meningitis. In the last named syndrome, marked symptomatic improvement may result from the use of large doses of the iodides. Iodides may be employed in combination with an arsphenamine or a heavy metal in late gummatous lesions in any location, in hepatic syphilis of all varieties, in cardiovascular syphilis and acute syphilitic meningitis, and to relieve pain promptly in bone syphilis. In all other forms of the disease, it is the practice to use iodides with the heavy metals and not during the courses of arsenical therapy.

Preparations and Doses. Either sodium or potassium iodide can be prescribed. Other iodide preparations have no special virtue. (For details of preparations, see page 618.) The drug can be given in tablet or capsule form, or in solution in water or syrup. The dose of iodides is extremely flexible and may be from one to four grams or more, three times daily. In acute syphilitic meningitis, the dose may be increased to as much as 50 grams daily, if the patient tolerates this amount. Similarly, large doses of iodides may be needed before beneficial effects are obtained in other granulomatous diseases, especially actinomycosis. The oral route is quite satisfactory. Iodides should be given before meals, well diluted with fluids.

The contraindications and intolerance to the iodides and their toxicity have been presented under the general pharmacology of this ion.

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CHAPTER 55

DRUGS USED IN THE CHEMOTHERAPY OF SYPHILIS

III. PRINCIPLES OF SYPHILOTHERAPY

The vigorous campaign conducted by the United States Public Health Service has called the attention of the physician as well as the public to certain basic facts concerning the prevalence and possibility of eradication of syphilis. It is estimated that more than 500,000 fresh cases of syphilis are reported to physicians in the United States yearly, that untold numbers remain unreported, that approximately 600,000 advanced cases which have never before received therapy report for the first time each year, and that five to 10 per cent of the population are infected. This is in sharp contrast to the low incidence of syphilis in Scandinavian countries where effective public health measures control the disease. It is estimated that 60,000 babies with congenital syphilis are born yearly in the United States, that 15 per cent of the blindness is due to syphilis, and that 10 per cent of the annual crop of insane is caused by central nervous system syphilis. No serious communicable disease except gonorrhea approaches these figures in regard either to incidence or economic loss (Parran, 1936; 1937; 1938). Early and correct diagnosis, prompt and efficient treatment, wider use of proved prophylactic measures and proper reporting of new cases provide the means by which syphilis may be reduced to a minor position in the list of public health problems.

The difficulty lies not in a lack of information but in the failure both of the physician and the public to use the knowledge already available. The renaissance of interest in syphilis which occurred between 1905 and 1910 was brought about through the discovery of the causative organism by Schaudinn, the diagnostic serological test by Wassermann and the potent antisyphilitic drug, arsphenamine, by Ehrlich. By the proper use of these three aids, the two objectives of therapy of early syphilis—control of infectiousness and radical cure—can be realized. For example, the dark field examination allows recognition of the disease days or weeks before the Wassermann test is positive and permits institution of therapy during the seronegative primary stage, the period of "golden opportunity." The routine use of the Wassermann test reveals 44 cases of syphilis in every 1000 individuals, whereas if this test is performed only when the disease is suspected, more than 98 per cent of these cases escape recognition. Again, the use of arsphenamines in early syphilis insures rapid control of infectiousness and best chances for radical cure.

Curability of Syphilis. The concept of curability of syphilis varies with the stage of the disease. *Biological or radical cure* signifies eradication of the last treponeme from the body and applies only to early (primary and secondary) syphilis. *Symptomatic cure* applies to late syphilis and signifies the disappearance of all signs and symptoms of the disease and the lack of infectiousness. The organisms are not all killed. The serology may be positive or negative, a matter of secondary importance. Cure, in either sense, can be determined only by careful observation over a period of years.

The *prognosis of untreated syphilis* is evident from the data obtained by Bruusgaard (1929) on patients who had gone untreated for as many as 40 years after infection. These cases were those of Boeck, chief of the syphilis clinic of Oslo, who, before the discovery of arsphenamine, was so skeptical of the results being obtained from mercury and iodides that he decided to allow his patients to go untreated and rely only on their own defense mechanisms. Bruusgaard was able to trace and study 309 cases (of the original 2000 patients) and to ascertain the cause of death in 164 others. He found that about 30 per cent had undergone a spontaneous cure, that approximately 60 per cent passed through the entire period without serious inconvenience, that only 10 per cent developed late nervous system syphilis and another 10 per cent cardiovascular involvement. Although these results are less favorable than those obtained by the Cooperative Clinical Group in the United States with *adequate* antisyphilitic therapy, it does emphasize that *no treatment at all may be much better than poor therapy.* Poor therapy allows a high incidence of serious late lesions, and these appear earlier than they would otherwise. Furthermore, infectious relapses and serious neurorecurrences are the price of poor treatment. The chance of the patient curing himself by his own immunological defense mechanisms is decreased by 50 per cent through inadequate medication. There is some evidence, however, obtained by Vonderlehr and associates (1936) from a study of Negroes in the southern part of the United States, that even inadequate treatment may be superior to no therapy. Nevertheless, the evidence justifying the modern systematic treatment of early syphilis is abundant and convincing.

Principles and Aims of Modern Therapy of Early Syphilis. The aim of therapy of early syphilis is biological cure, as defined. The results obtained vary directly with the stage of syphilis during which medication is started. The possibility of obtaining a biological cure is as follows:

PERCENTAGE OF BIOLOGICAL CURABILITY

Stage of Syphilis	*Best Therapy*	*Average of All Kinds of Therapy*
Seronegative Primary	95–100%	72%
Seropositive Primary	90–95	54
Secondary	80–90	50

These data emphasize emphatically the need for efficient and early treatment. Inasmuch as *medication is never started without the diagnosis of syphilis being assured,* early diagnosis becomes essential. *Early diagnosis of syphilis is a laboratory, not a clinical procedure* and involves serological tests and efficient use of the dark field microscopic examination. The latter often allows the diagnosis to be made weeks in advance of positive serological tests. *The non-syphilitic nature of every genital sore, regardless of its apparent innocence, can be established only by repeated dark field and serological examinations.*

The treatment of *early syphilis* must be focused on the most resistant patient and the most resistant organism (Moore). The vigorous and routine medication which this necessitates is possible because most patients are young and otherwise healthy, and the biology of the early stages of the syphilitic infection is similar in all cases. In other words, although each patient is handled as an individual medical problem, in many respects the disease itself and not the patient is treated. In *late syphilis,* in marked contrast, the patient and not the infection is primarily treated because the individuals are older and have various degenerative processes due to age, disease or the syphilitic infection. In such patients, one must avoid the "therapeutic paradoxic," first described by Wile, of improving the disease but not the patient. This results from too vigorous arsenical therapy in late syphilitic involvement of a vital organ, causing such rapid involution of the lesions that serious functional disturbances occur. This is seen especially in complicated cardiovascular syphilis.

Routine Modern Therapy of Early Syphilis. The modern therapy of early syphilis owes its inception to the investigations of Almkvist (1920, 1926) and Moore and Keidel (1926). The latter workers developed their method of treatment in the syphilis clinic of the Johns Hopkins Hospital in the years 1916 to 1917. It has been adopted by the Cooperative Clinical Group and is in general employment throughout the country. The major features of this routine are presented in Table 51. It consists of the use of courses of an arsphenamine or mapharsen alternating with courses of a heavy metal, preferably bismuth. *Continuous treatment without rest periods* is absolutely essential for a full year after the blood and spinal fluid Wassermann have become permanently negative. This is followed by a rigidly controlled year of probation, which in turn is succeeded by a lifetime of careful observation and periodic physical and serological examinations. The distinct advantages of continuous treatment without rest periods over intermittent therapy in early syphilis are apparent from the results obtained by the Cooperative Clinical Group (*see* Stokes and Usilton, 1937). To cite but one example, the introduction of a rest period of one month or more during the first year of therapy reduces the number of serological negatives from 68 per cent to 40 per cent.

Naturally, *treatment is never started unless the diagnosis is absolutely certain* and a base line medical examination is performed. If an arsphenamine is used prior to adequate diagnosis of the disease, the patient must then be treated exactly as if he had syphilis.

The arsenical of choice may be mapharsen, arsphenamine itself, neoarsphenamine or silver arsphenamine. The bismuth preparation may be an insoluble drug suspended in oil, or a water or oil-soluble compound. The more rapidly absorbed preparations must be given two or three times a week and the resulting expense and inconvenience make this difficult for most patients. The alternating courses of arsenic and bismuth protect the patient against the cumulative toxicity from either compound, attack the organism from two directions, and prevent the treponemes from becoming resistant ("fast") to either chemical. The use of bismuth with the first few doses of arsenic at the initiation of treatment (Table 51) helps to lower the incidence of neurorecurrences. Otherwise, the two drugs are used in alternation, not together. When early syphilis is treated by the continuous concurrent use of an arsphenamine and bismuth, instead of alternating the drugs, the results are inferior (Bechk and Barnett, 1939).

The details of the modern therapy of early syphilis and the results to be expected from it must be sought elsewhere. (*See* Moore, 1933, 1936; Stokes, 1934; Cole, 1936; also publications of Moore, Stokes, Cole, and Clark, and their respective associates, in Venereal Disease Information, 1929, 1932, 1934, 1938.)

Massive Short-Term Arsenotherapy of Early Syphilis. An attempt to treat primary and early secondary syphilis by means of massive doses of neoarsphenamine or mapharsen

TABLE 51

A SCHEME OF ROUTINE TREATMENT FOR EARLY SYPHILIS

DAY OR WEEK	ARSPHENAMINE	INTERIM TREATMENT	BLOOD WASSERMANN REACTION	REMARKS
Day	Gm.			
1	0.3–0.6	Bi. 0.2 Gm. may be given simultaneously with first 4 doses of arsphenamine. Helps to prevent neurorelapse	1	Arsphenamine dosage for first 3 injections at level of 0.1 Gm. for each 25 lbs. body weight. Average subsequent dosage, 0.4 Gm., men; 0.3 Gm., women. In average patient all lesions heal rapidly and blood Wassermann reaction becomes negative during first course. If arsphenamine cannot be used, substitute 8 to 10 doses 0.3 Gm. silver arsphenamine, or 10 to 12 maximum doses 0.9 Gm. neoarsphenamine. This applies also to subsequent courses. Mapharsen may be used in maximal doses of 0.04 Gm., female; 0.06 Gm., male.
5	0.3–0.6			
10	0.3–0.6			
Week				
3	.4			
4	.4			
5	.4			
6	.4			
7	.4			
8		Bi., 4 doses 0.2 Gm., and KI., or Ung. Hg. and KI.	1	If mercury is used, allow overlap of 1 week at end of first and start of second arsphenamine courses. No overlaps necessary with bismuth. At this point a few days without treatment may be dangerous (neurorecurrence).
9				
10				
11				
12	.4		1	Arsphenamine starts, bismuth stops. Watch for provocative Wassermann reaction after first dose of arsphenamine. Try to prevent short lapses in treatment, especially at this early stage.
13	.4		1	
14	.4			
15	.4			
16	.4			
17	.4		1	
18–23		Bi. 6 doses, or Ung. Hg. and KI.		Bismuth is better than mercury. Use it if possible. Examine cerebrospinal fluid routinely at about this time.
24	.4			
25	.4			
26	.4			
27	.4			
28	.4			
29	.4			
30–37		Bi., 8 doses or Ung. Hg. and KI.		Mercury inunctions may be substituted for bismuth if patient's finances or occupation demand it.
38	.4		1	
39	.4			
40	.4			
41	.4			
42	.4			
43	.4		1	Patients with seronegative primary syphilis may cease treatment here, if blood serologic test has always been negative.
44–53		Bi., 10 doses or Ung. Hg. and KI.		Note that bismuth or mercury courses are gradually getting longer—4, 6, 8, and now 10 weeks.

TABLE 51 (*Continued*)

DAY OR WEEK	ARSPHENAMINE	INTERIM TREATMENT	BLOOD WASSERMANN REACTION	REMARKS
54	.4		1	The average seropositive primary or early secondary patient should have at least 5 courses of arsphenamine.
55	.4			
56	.4			
57	.4			
58	.4			
59	.4		1	It is safer to finish treatment with bismuth or mercury rather than with arsphenamine.
60–69		Bi., 10 doses or Ung. Hg. and KI.		
70–122	Probation	No treatment	6–12	Blood Wassermann every month if possible; at least every other month.
123	Complete physical and neurologic examination, spinal puncture, and, if possible, fluoroscopic examination of cardiovascular stripe. Thereafter, yearly physical examinations and blood Wassermann every 6 to 12 months. If the two spinal fluid examinations above are negative this need not be repeated, and the possibility of central nervous system syphilis is very remote.			

given over a period of a few days by the continuous intravenous drip method, without additional or subsequent antisyphilitic therapy, has been reported by Chargin, Hyman, Leifer and their coworkers (1939). The treatment involves the intravenous injection of five to six times the usual maximum therapeutic dose of neoarsphenamine or 10 to 15 times the comparable dose of mapharsen during a period of four to five days. The injection continues for 15 hours daily. The immediate clinical and serologic results obtained in a limited series of patients (394) were quite favorable. However, the incidence of untoward reactions was high, particularly peripheral neuritis, fever, hemorrhagic encephalitis, and toxicodermas.

The great public health and economic advantages of such therapy are evident, but considerably more controlled clinical and experimental study is required to determine the late clinical results to be expected from the short-term technic in comparison with the accepted routine of prolonged continuous treatment, and to ascertain the hazards of the toxic reactions. Nothing is known as yet of the possible effects of this new method in various forms of late syphilis. Nor is it determined whether the five day period is optimal or whether other arsenicals, less useful under the conventional system of therapy, might be more advantageous and less toxic by the short-term technic. The treatment requires one week of full hospitalization. It must be emphasized that massive short-term chemotherapy cannot be recommended for general use at present, and that it is still in the experimental stage. The history and clinical status of this treatment have been reviewed critically by Moore and Mohr (1939) and by the Council (Report of the Council, 1940). Likewise, many aspects of this new technic have been reviewed by several members of the Committee on Massive Drip Intravenous Therapy in a *Symposium* (1940).

Principles of Therapy of Latent Syphilis. Any syphilitic infection of less than four years' duration must be treated exactly as early syphilis. Clinically, latent syphilis refers to the infection which has been present for more than four years combined with the absence of physical signs and symptoms of the disease. The only evidence for its existence is a positive serological test of the blood. Cerebrospinal fluid examination and teleoroentgenographic and fluoroscopic examinations of the heart and aorta are necessary to rule out clinically unrecognizable involvement of the nervous system and cardiovascular apparatus.

The object of therapy in latent syphilis is no longer biological cure but prevention of infectious relapses and progression of the disease. Neoarsphenamine, silver arsphenamine or mapharsen is selected instead of arsphenamine and the dose is reduced about one-third from that used in early syphilis. Eight to ten weekly injections of arsenic are followed by eight to ten weeks of bismuth medication, preferably with the subsalicylate. This alternation is continued until 25 to 30 injections of each drug have been given. The iodides are used with the courses of heavy metal. During the second year of medication, therapy is not so urgent and reliance is placed on bismuth (three courses of 10 to 12 injections each) alternating either with rest periods or with mercurial rubs. Rest periods at this stage do no harm and further treatment must be individualized in latent syphilis due to the great variability of the clinical and serological responses.

It is important to remember that *a woman with latent syphilis has only one chance in six of bearing a healthy child.* Five of six pregnancies terminate in abortion, stillbirths, or congenitally syphilitic offspring. In the United States, 60,000 babies with congenital syphilis are born annually. In no other field of medicine will the investment of a small amount of time and medication yield such huge dividends as in the proper therapy of syphilis during pregnancy. *A routine serologic test on every pregnant woman is essential.* Pregnant women tolerate antisyphilitic treatment quite well. In early pregnancy, 0.2 to 0.4 gram of arsphenamine or its equivalent should be given weekly for 12 to 15 weeks. This is followed by 10 weekly injections of a relatively insoluble bismuth preparation, in amounts which yield from 50 to 100 mgm of metallic bismuth in each dose. Treatment is continuous and without rest periods and is so planned that a few doses of an arsphenamine or mapharsen are given just before delivery. In late pregnancy, arsenical and bismuth therapy are combined. Treatment during pregnancy is for the child. After delivery, treatment of the mother is continued in a manner appropriate for her type of syphilitic infection. The infant is examined for evidences of syphilis by means of the cord Wassermann, the placental histology, the radioscopic study of the skeleton and a pediatric follow-up for six months. The details of therapy of the *pregnant syphilitic woman* and of *congenital syphilis* may be obtained from the several references cited and from the publications of Cole and associates (1936, 1937). It may be stated, however, that the oral use of acetarsone is not to be recommended in congenital syphilis and that the drug is contraindicated and perhaps even dangerous in the therapy of any form of syphilis (Cole, 1936, 1937; Rosahn and Kemp, 1937; Pillsbury and Perlman, 1939; Robinson and Robinson, 1939).

Principles Underlying Therapy of Serious Forms of Late Syphilis. The serious forms of late syphilis refer especially to cardiovascular syphilis and neurosyphilis. The more benign forms, such as the cutaneous and osseous, are treated much the same as is latent syphilis. The management of tertiary syphilis of the heart and nervous system is so specialized that it should be undertaken only by one who has had considerable experience in this field. The details may be found in the previously cited references. It is intended here mainly to emphasize the fact that therapy is strikingly different from that for early or latent syphilis, that the patient rather than the infection is to be treated, and that the object of therapy is to arrest the disease if possible, relieve symptoms, prolong life beyond the expected duration, and do no harm to the patient by overzealous medication.

In *cardiovascular syphilis,* which is uncomplicated, *old arsphenamine is strictly contraindicated* and initial mild therapy with bismuth and iodides should precede an arsenical by at least three months, in order to prevent therapeutic shock. When arsenicals are started, the initial dose should not exceed the equivalent of 50 mgm, or the eventual dose the equivalent of 0.3 gram, of neoarsphenamine. Treatment must be continued without interruption for at least two years regardless of serological progress, and preferably for from four to eight years. It consists of alternating arsenical and heavy metal, given in long courses of 10 to 12 weeks each. If a rest from medication is absolutely necessary, it should come after a course of heavy metal. If the patient has a complication of cardiovascular syphilis (aortic regurgitation, aneurysm, narrowed coronary ostia), treatment must be much milder. If congestive failure is present, compensation must first be restored by rest in bed and digitalis. Then small doses of bismuth are given with iodides. If cardiovascular reserve is low, the case may never be suitable for arsenical therapy. *Adequate therapy of early syphilis prevents cardiovascular syphilis, and proper treatment of the latter in its early stages prevents complications and reduces mortality by 67 per cent.*

Syphilis of the *central nervous system* takes many forms and therapy is determined by the relative involvement of the neural substance itself, the meninges and the blood vessels. Vascular or meningitic complications usually require preliminary use of bismuth and iodides. If these complications are absent and the disease is in its early stages, therapy is more like that of early syphilis. *Fever therapy,* especially *malaria,* finds special usefulness in paresis and certain other types of central nervous system syphilis but its use requires considerable experience. *Syphilitic optic atrophy* responds best to inoculation malaria or to subarachnoid (suboccipital) Swift-Ellis therapy (Moore, Woods and Hopkins, 1938). Tryparsamide is also useful before or after malaria and in all forms of neurosyphilis (except optic atrophy) with resistant spinal fluid serology. Unless good treatment can be given by the general practitioner, he will do wisely to leave this difficult field of therapy to the expert.

USES OF THE ARSPHENAMINES AND ARSENOXIDE FOR DISEASES OTHER THAN SYPHILIS

In certain infections other than syphilis, the arsphenamines are useful. In cases of *pulmonary abscess* or *gangrene* due to Vincent's organisms or other spirochetes, the arsphenamines given intravenously are often effective. In *Vincent's angina,* arsphenamine itself may be applied locally to the oral lesions in the form of the powder or in 10 per cent strength in glucose or glycerin solution. Mapharsen, as a powder or in 0.5 to 1.0 per cent aqueous solution, may likewise be applied locally. Mapharsen has also been employed locally in the treatment of *Trichomonas vaginalis vaginitis.*

In *yaws,* as in syphilis, the arsphenamines are agents of choice. The disease yields to treatment much more readily than does syphilis. It is not true, however. that *one* dose is all that is required in yaws. Three to six weekly injections provide a minimum of therapy. Bismuth is also effective when given once weekly for six injections. In *relapsing fever,* the arsphenamines given at the *onset* of a paroxysm are quite effective and specific. Several full doses may be required.

Promising results have been reported from neoarsphenamine in *anthrax.* Likewise, neoarsphenamine appears to be of value in the treatment of urinary tract infections due to micrococci, streptococci and staphylococci (Buchtel and Cook, 1940). The use of the antisyphilitic arsenicals in *malaria* and *undulant fever* is not based on exigent clinical evidence, although tertian inoculation (therapeutic) malaria appears to yield quite readily to the arsphenamines and especially to mapharsen (Goldman, 1938). Quartan malaria of the inoculation type, however, is not cured by mapharsen although symptoms are relieved (Young and McLendon, 1939).

The use of atoxyl in *African sleeping sickness* is described on page 955.

Tryparsamide is also of value in the treatment of African sleeping sickness. Pearce (1939), in her summary of the results of the eleven year (1927–1937) campaign against the disease in the Belgian Congo, states that tryparsamide is being increasingly used and that it is the only drug known which is capable of curing both early and advanced cases.

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CHAPTER 56

SULFANILAMIDE AND RELATED SULFONAMIDE DRUGS

I. THE PHARMACOLOGY OF SULFANILAMIDE

It is difficult to overestimate the importance for medicine and public health of the discovery of sulfanilamide and related chemotherapeutic agents. These drugs represent the only known chemicals capable of curing serious systemic bacterial infections in man in doses allowing a satisfactory margin of safety. Within the space of a few years, many diseases with high mortality rates have been successfully treated with sulfanilamide or its congeners; chemotherapeutic research has undergone a renaissance; more than twelve hundred organic compounds containing sulfur have been synthesized and tested, and a new field for the study of the relationship between chemical structure and specificity of antibacterial action has been developed. The ultimate ramifications of these discoveries cannot yet be predicted.

The following discussion deals especially with *sulfanilamide, sulfapyridine,* and *sulfathiazole* because these three drugs are most widely employed clinically and experimentally in the United States at present and are the agents concerning which most information has been obtained. Other sulfonamide derivatives having therapeutic interest or promise will be mentioned when the information they provide is appropriate.

Historical. Although para amino benzene sulfonamide (sulfanilamide) was first prepared in 1908 by Gelmo in the course of his investigations on azo dyes, a quarter of a century was to pass before its utilization for the chemotherapy of human bacterial infections. An interesting chain of circumstances led to the final discovery of its therapeutic value.

In 1909, Hoerlein and coworkers, of the I. G. Farbenindustrie, synthesized the first azo dyestuffs containing sulfonamide and substituted sulfonamide groups and noted them to be superior in color-fastness to similar dyes without the sulfonamide group. The firm combination which the complex azo dyes formed with proteins of wool and silk suggested the possibility that these agents might react with bacterial protoplasm, and in 1913 Eisenberg discovered the bactericidal action *in vitro* of *chrysoidine* and suggested its use in chemotherapy. In the following year, Tchichibabin and Zeide (1914) synthesized a red dye *pyridium* from chrysoidine, which subsequently was to be introduced as a urinary antiseptic (Ostromyslensky, 1926). In the years immediately following, *scarlet red,* another azo dye, came into prominence and chemical advances in the synthesis of azo dye derivatives of cupreines were made by Jacobs and Heidelberger (1917) and Heidelberger and Jacobs (1919). The same investigators also prepared para amino benzene sulfonamide according to the method of Gelmo and postulated that this substance would be liberated by the breakdown in the tissues of sulfonamido chrysoidine. Although they commented on the high bactericidal potency of their compounds, unfortunately the work was not continued. In 1930, another azo compound known as *serenium* (2–4 diamino 4′ ethoxy azo benzene) was introduced by Ostromyslensky as a urinary antiseptic.

Investigations of chemists at the I. G. Farbenindustrie resulted in 1932 in the issuing of a German patent to Klarer and Mietzsch covering *prontosil* (the hydrochloride of 4′ -sulfonamido-2, 4 diamino-azobenzene) and several other azo dyes containing a sulfonamide group. In the same year, Domagk, director of the pathological laboratory in Elberfeld, Germany, working with Klarer and Mietzsch, observed that mice with streptococcal septicemia could be protected by prontosil and that the drug was effective in certain other experimental infections in laboratory animals (Domagk, 1935). To Domagk belongs the credit for the discovery of the chemotherapeutic value of prontosil, for which he received recognition by being awarded the Nobel Prize in Medicine for 1938. In 1933, the first clinical case study was reported by Foerster who gave "streptozon" (prontosil) to a ten-month old infant with staphylococcal septicemia and obtained a dramatic cure. In a second communication, Domagk (1935) described the use of prontosil in experimental and clinical streptococcal infections and announced a new chemotherapeutic azo dye called *prontosil-S* (*prontosil-soluble,* later called *neoprontosil;* the disodium salt of 4′ sulfonamido-phenyl azo 1-oxy-7-acetylaminonaphthalene-3, 6 disulfonic acid). Other clinical case studies began to appear and it was established early in 1935 that prontosil was highly effective clinically in hemolytic streptococcal infections.

In France, Levaditi and Vaisman (1935), working with prontosil (prepared for them by Girard and called *"rubiazol"*), confirmed the experiments of Domagk on mice infected with hemolytic streptococci, and laid emphasis on the stimulation by the drug of the phagocytic powers of the host. The Tréfouëls, Nitti and Bovet (1935), working with Fourneau at the Pasteur Institute in Paris, soon communicated the important finding that in the tissues of the host the azo dyes were split at the azo linkage and that prontosil thus yielded para amino benzene sulfonamide, which they thought to be the chemotherapeutic portion of the molecule. Fourneau then prepared this compound and it was shown by him and his associates (1936) that para amino benzene sulfonamide was as effective in curing experimental infections as was prontosil. Goissedet and associates (1936) reported similar findings. This was a discovery of major importance.

No great attention was paid in the medical literature to these epoch-making advances in chemotherapy until the interest of English investigators was aroused. In 1935, Buttle reported that prontosil was effective in streptococcal infections in mice. Colebrook and Kenny (1936) communicated their experimental observations in mice and clinical results with prontosil in puerperal sepsis, in which disease they obtained a definitely beneficial effect. Buttle, Gray and Stephenson (1936) confirmed the finding that para amino benzene sulfonamide was active in hemolytic streptococcal infections in mice and also curative of meningococcal infections. These two reports awakened the interest of the medical profession to the new field of bacterial chemotherapy, and experimental and clinical articles in great profusion soon appeared.

In the United States, three groups of investigators in particular were associated with the early studies of the prontosils and para amino benzene sulfonamide—Long and Bliss and Marshall and associates at the Johns Hopkins Hospital and Medical School; Mellon, Gross and Cooper of the Institute of Pathology of the Western Pennsylvania Hospital (Pittsburgh), and Rosenthal and Bauer at the National Institute of Health. Long and Bliss confirmed the fact that para amino benzene sulfonamide is the effective portion of the prontosil molecule and proposed that it acts by exerting a bacteriostatic rather than a bactericidal effect on microorganisms. The basic contributions to the pharmacology and toxicology of para amino benzene sulfonamide were made by Marshall and his collaborators (1937, *et seq.*). The Council on Pharmacy and Chemistry of the American Medical Association reported on para amino benzene sulfonamide in 1937, suggested that it be given the name *sulfanilamide* and accepted the drug for inclusion in N.N.R.

The use of sulfanilamide was soon extended to the chemotherapy of infections other than those due to hemolytic streptococci, and numerous derivatives of sulfanilamide were developed and tested for their clinical value in various bacterial, protozoal and virus diseases. Para benzyl amino benzene sulfonamide (*benzyl sulfanilamide, septazine*) was synthesized by Goissedet and coworkers (1936) and has had an extended clinical trial in France. Rosenthal and associates (1937, *et seq.*) synthesized and studied a large number of new compounds, including *sulfanilyl sulfanilamide* (*di-sulfanilamide; disulon*) which, with its dimethyl derivative (*uliron*) synthesized by Domagk (1937), has been widely employed for gonococcal infections particularly in Germany. The most promising of the numerous congeners of sulfanilamide is *sulfapyridine,* synthesized in England by Ewins and Phillips and first reported by Whitby (1938) to have value in pneumococcal and staphylococcal infections in mice. Soon thereafter, sulfapyridine was shown to produce dramatic results in human pneumococcal pneumonia. In 1939, Fosbinder and Walter, and Lott and Bergeim prepared *sulfathiazole* and this drug and its methyl derivative have been studied experimentally and clinically for their value in staphylococcal, pneumococcal and other infections.

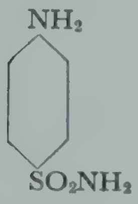
The reader interested in the details of the historical aspects of this important group of drugs is referred especially to Schulte (1938) and Long and Bliss (1939).

Terminology and Chemistry. The simultaneous development of the organic sulfonamide derivatives in industrial research laboratories has resulted in considerable confusion in terminology due to the application to the same drugs of different patented trade names. *Prontosil,* the first of the group to be discovered, was too insoluble for parenteral injection in solution, and *prontosil-S* (*prontosil-soluble,* later called *neoprontosil*) was then synthesized. Both drugs were employed in countries other than Germany under a variety of trade names. *Prontosil-soluble* was first marketed in the United States as "prontosil," a circumstance which complicated an already confused situation. The demonstration that the active part of the molecule is para amino benzene sulfonamide and the adoption by the Council of the non-proprietary name *"sulfanilamide"* established order in the field. The U.S.P. XI (Second Supplement, 1939) includes *Sulfanilamide* as an official drug.

The structural formulas of sulfanilamide, prontosil, prontosil-soluble and the more important related sulfonamide drugs are given in Table 52 with some of their more commonly employed trade names. It is urged that only official or Council-accepted preparations and terms be employed for the best interests of the patient and the future development of this important field. The preparations available for clinical use will be described.

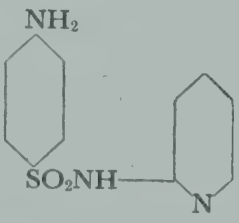
Relationship between Chemical Constitution and Antibacterial Action. The data available in the complex and rapidly developing field of the organic sulfonamide drugs are too meager to allow a comprehensive analysis of the relationship between chemical structure and chemotherapeutic activity. Certain general principles, however, may be pointed out. Early in the study of the antibacterial action of prontosil, J. and Mme. J. Tréfouël and coworkers (1935) demonstrated that the azo linkage ($-N=N-$) was unnecessary for bactericidal effects, prontosil being split in the tissues at this linkage to yield sulfanilamide. They proved the chemotherapeutic value of sulfanilamide and found that the sulfonamide group ($-SO_2NH_2$) must be attached to the benzene ring in order for the compound to be potent. The azo dyes were thus antibacterial by virtue of yielding sulfanilamide. Adequate confirmation of these basic findings was soon forthcoming. Bliss and Long (1937) reduced prontosil-soluble with cysteine hydrochloride and showed the resulting compound (sulfanilamide) to be active against hemolytic streptococci, whereas the original molecule lacks this property *in vitro*. Interest therefore rapidly shifted from the azo dyes to sulfanilamide itself, and most of the subsequent experimental and clinical investigations have been conducted with sulfanilamide or derivatives of it. Nevertheless, there is some evidence that in certain of the complex azo dyes the azo linkage *per se* may play an important rôle in drug action.

Table 52



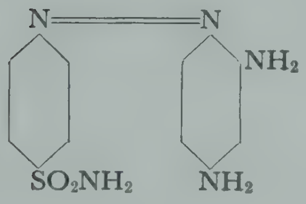
Sulfanilamide, U.S.P.

Prontylin
Streptocide
Prontosil album
Sulfamidyl
Lysococcine
Stramid



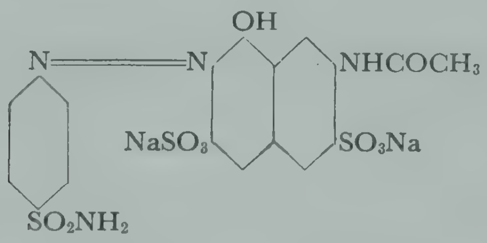
Sulfapyridine, N.N.R.

M & B 693
Dagenan



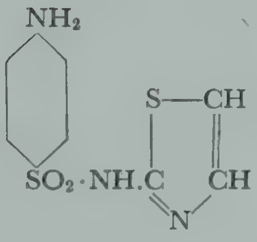
Prontosil

Prontosil flavum
Prontosil rubrum
Rubiazol

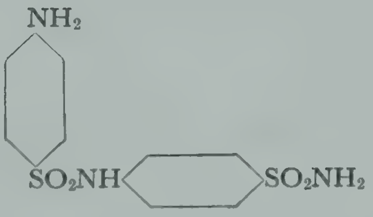


Neoprontosil (Prontosil-Soluble)

Prontosil-S
Prontosil solution
Prontosil red
Streptozon

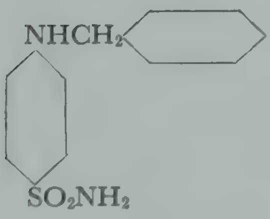


Sulfathiazole



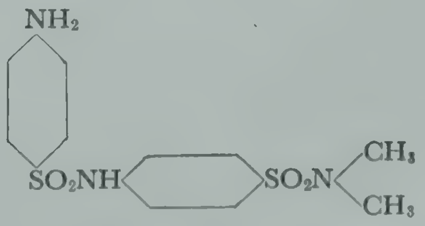
Sulfanilyl Sulfanilamide

Disulon



Benzyl Sulfanilamide

Septazine
Proseptazine



Sulfanilyl Dimethyl Sulfanilamide

Uliron
Uleron

Regarding sulfanilamide itself and its immediate derivatives, it may be said that sulfur is an indispensable part of the molecule. The sulfonamide group is not essential for antibacterial potency, but rather the para linkage of the sulfur appears to be the important feature. For example, the compound 4, 4′ diaminodiphenylsulphone, obtained by substituting p-phenylamine for the amide of sulfanilamide, is said to be 100 times more potent against experimental streptococcal infections than sulfanilamide itself (Buttle and associates, 1937), and mercaptans, disulfides, sulfinic and sulfonic acids, sulfoxides and sulfones containing an aromatic nucleus have all been found to possess antistreptococcal activity (Fourneau and associates, 1938; Gley and coworkers, 1937). Most of the active compounds contain an amino, substituted amino or nitro group in the position para to sulfur.

In sulfanilamide the para amino group is essential, and if it is replaced by another group or shifted to the ortho or meta position, considerable reduction in potency results. The meta compound, in addition, is much more toxic (Laug and Morris, 1939). The only changes in the para amino group of sulfanilamide which do not decrease or destroy chemotherapeutic activity are those which still allow the body to form the amino compound (such as a nitro group or the azo linkage) or which represent active oxidation products of sulfanilamide (such as hydroxylamine). The sulfonamide group of sulfanilamide may undergo a variety of changes provided the resulting compounds yield sulfonic acid on oxidation. The sulfonic acid group increases solubility and tends to raise oxidation-reduction potentials (Shaffer, 1939). Substitutions made in the amide nitrogen may have no effect on the antibacterial activity of the molecule (methyl or ethyl substitutions), may decrease it (higher alkyl groups) or increase it (p-aminophenyl or p-nitrophenyl groups). Addition of a third group to the ring of sulfanilamide, as a rule, causes a diminution of potency. The acetyl derivative of sulfanilamide is almost completely inactive *in vitro* and *in vivo*. More complex derivatives such as sulfanilyl sulfanilamide, the dimethyl derivative of sulfanilyl sulfanilamide and sulfapyridine have also been found to possess considerable chemotherapeutic activity. Sulfapyridine, for example, is much more effective against pneumococci and certain other microorganisms than is sulfanilamide. Sulfathiazole and sulfamethylthiazole also possess clinical value in certain types of bacterial and virus infections. Lastly, organic compounds analogous to the sulfones but containing arsenic, phosphorus or carbon instead of sulfur have been found to exert antibacterial action (Rosenthal, 1939).

The foregoing examples are cited to illustrate the complexity of the field and to indicate the lines of research that are being developed. The chemical basis of antibacterial specificity cannot be stated, and the differences in potency of various sulfonamide drugs against different bacteria may be quantitative rather than qualitative in nature. Marshall (1939) has outlined the difficulties inherent in this field of investigation, and the interested reader is referred to his review, to the monograph by Mellon and associates (1937), and to the reviews of Kolmer (1940) and Northey (1940).

Action in Vitro Against Bacteria. Domagk noted in his original communication that prontosil was quite inactive against bacteria *in vitro* and exerted its antibacterial effects only in the animal organism. Indeed, if Domagk had not conceived that chemicals ineffective in the test tube might still be bactericidal *in vivo* the discovery of the sulfonamide drugs might have been appreciably delayed. It is generally agreed today that the prontosils are active only in the body and that even high concentrations *in vitro* are inactive against microorganisms. Sulfanilamide, however, is an effective agent *in vitro,* and there is a direct correlation, with a few exceptions, between the *in vivo* and *in vitro* actions of sulfanilamide on bacteria. This allows the anticipation that diseases caused by those microorganisms against which sulfanilamide has an appreciable effect in the test tube will respond in some measure to sulfanilamide therapy.

An abundant literature has accumulated in the few years since the discovery of prontosil concerning the actions of the sulfonamide drugs *in vitro* against a variety of bacteria. Much of the available data is conflicting and requires confirmation, classification, and discerning interpretation because of the many different technics that have been used by various investigators, which prevent direct comparison of the results obtained, and the multitude of factors which control the *in vitro* effects of sulfanilamide. The major factors are the age and virulence of the bacterial culture examined, the size of the inoculum, the type of nutrient medium employed with special reference to the presence or absence of serum, blood, leukocytes and certain peptones, the duration of the experiments, the temperature of the environment and finally the concentration of the drug employed.

Despite the complexities suggested, certain conclusions stand out clearly. Sulfanilamide in a concentration of 1:10,000 is *bacteriostatic* for *hemolytic streptococci* with a few exceptions (notably Group D of Lancefield) when the medium is a favorable one, such as peptone broth or beef infusion. In higher concentrations (1:1000 to 1:250) a bactericidal action may be noted. The addition of whole blood to the medium enhances the possibility of a bactericidal effect due particularly (if not entirely) to the phagocytic action of leukocytes. In 1:10,000 concentration, sulfanilamide also inhibits the growth of *pneumococci, meningococci, gonococci, Cl. Welchii* and *Brucella melitensis.* When the culture medium is less favorable for growth and higher concentrations of sulfanilamide are employed, a bacteriostatic or even a bactericidal effect can be observed against *staphylococci* (Spink, 1939) and a number of *Gram negative bacilli.* This constitutes the basis for the therapeutic use of sulfanilamide in infections of the urinary tract because urine is a poor growth medium, and high concentrations of drug are attained in urine after systemic administration. The many details of the *in vitro* actions of sulfanilamide are beyond the scope of this discussion. An authoritative presentation may be found in the monograph by Long and Bliss (1939), and in the review by Kolmer (1940).

Action in Vivo Against Experimental Infections. Sulfanilamide and a number of related sulfonamides are capable of curing a large number of bacterial diseases in a variety of animals. The results obtained are often transferable to human infections, and animal experimentation thus provides a means of preliminary investigation of the clinical value of these new chemotherapeutic agents. Most of the *in vivo* laboratory experiments with sulfanilamide have been performed with white mice, a species which fortunately is highly susceptible to a large number of bacterial and virus infections to which man is heir. Despite the availability of a standard test animal, experimental results have often been discordant, chiefly due to the lack of an accepted standard technic for the testing of new compounds in infections in mice. Standardized methods for producing streptococcal infections and testing chemotherapeutic agents have been proposed by Long and Bliss (1939), Litchfield, White and Marshall (1939), and others.

The literature on the efficacy of sulfanilamide and its derivatives in experimental infections has been extensively reviewed by Long and Bliss (1939) and Kolmer (1940).

Streptococci. Streptococcal infections in mice have naturally received much attention by numerous investigators. The factors controlling the results obtained are as complex as those described previously for *in vitro* experiments. Sulfanilamide, for example, can protect mice against 10,000 minimal lethal doses of virulent or moderately virulent streptococci. Animals which recover show no immunity to the organism and can be reinfected, as first demonstrated by Nitti and Bovet (1936) and later confirmed by others. When streptococci of low virulence are used to cause infections of the mouse, however, sulfanilamide is valueless. As suggested by Long and Bliss, this is probably due to the necessity for using large inocula (often 100 million organisms) in order to produce death, and, as is the case also in *in vitro* experiments, the antibacterial action of sulfanilamide decreases as the size of the inoculum increases. The strain of streptococcus employed is also of major importance. Infections in mice induced with Group A hemolytic streptococci (Lancefield's classification) are readily amenable to sulfanilamide therapy. Inasmuch as Group A includes most of the strains causing human infections, the results obtained in mice with Group A organisms are more capable of being transferred to human therapeutics. Infections in mice induced by Group B (bovine and human) strains of hemolytic streptococci are resistant to sulfanilamide therapy, and Group C strains (of animal origin) are moderately susceptible (Long and Bliss, 1939).

Sulfonamide compounds other than sulfanilamide also have chemotherapeutic value in experimental streptococcal infections in mice. These are too numerous to be included but it may be stated that one of the more promising drugs is 4, 4′ diaminodiphenylsulfone, the most active compound thus far tested. Its high toxicity, however, prevents its clinical use. The diacetyl derivative of the drug is said to possess considerable activity and to be less toxic (Buttle and associates, 1937; Fourneau and coworkers, 1937; Raiziss and collaborators, 1938). Sulfapyridine is more effective, on a weight basis, than sulfanilamide in curing experimental streptococcal infections in mice (Whitby, 1938; Long and coworkers, 1939). Species of animals other than white mice have been employed for experimental infections. These include white rats, guinea pigs, rabbits, dogs and monkeys, and the results in general corroborate the more complete data for mice.

Staphylococci. Although Domagk in his original report (1935) stated that prontosil cured staphylococcal infections in rabbits, the results obtained with sulfanilamide and several of its derivatives in the therapy of experimental staphyloccocal infections in mice have been disappointing (Mellon and collaborators, 1937; Feinstone and associates, 1938). Sulfapyridine and sulfathiazole, in contrast, appear to be effective. To date, therapy of experimental staphylococcal infections with sulfonamide drugs is less satisfactory than is the case for streptococcal infections.

Pneumococci. Rosenthal (1937) and Cooper and Gross and their associates (1937, 1938) have definitely established the chemotherapeutic value of sulfanilamide in experimental pneumococcal infections (types I, II, III) in mice and rats. The drug is effective against both pneumococcal pneumonia and pneumococcal meningitis. Numerous studies also have dealt with the combined use of sulfanilamide and type specific antisera. This combination therapy gives better results in type I and II infections in mice than either serum or sulfanilamide alone (Branham and Rosenthal, 1937; Long and Bliss, 1937). The beneficial effects of sulfanilamide are only striking, however, when large inocula of virulent pneumococci are avoided (Long and Bliss, 1937).

A number of sulfanilamide derivatives have also been examined for their efficacy in experimental pneumococcal infections. Diaminodiphenylsulfone exhibits definite superiority over sulfanilamide (Buttle and coworkers, 1937; Feinstone and associates, 1938). Sulfapyridine and sulfathiazole, however, are outstanding as the compounds most effective in their protective and curative effects in pneumococcal infections in mice. For example, they protect against 1000 minimal lethal doses of highly virulent and rapidly invasive type I, II or III pneumococci.

Meningococci. By the use of the technic of Miller (1935), it is possible to produce meningococcal infections in mice injected intraperitoneally with organisms suspended in mucin, thus allowing experimental evaluation of the sulfonamide drugs. Buttle and coworkers (1936) and Proom (1937) early established the efficacy of sulfanilamide in meningococcal infections, and the latter worker noted that the drug prevented meningococcemia and sugested its use in clinical infections. It is not clear whether the combined use of sulfanilamide and antiserum yields potentiative or merely additive effects in experimental infections (Branham and Rosenthal, 1937; Brown, 1937). Sulfapyridine appears to be at least as active against meningococci as is sulfanilamide (Whitby, 1938; Feinstone and associates, 1938). Long and Bliss (1939), from their experience in the preliminary testing of more than 200 sulfur-containing organic compounds in experimental meningococcal and streptococcal infections in mice, observed that certain drugs which had only a minimal effect in streptococcal infections were quite active against meningococci, but the reverse was never noted. These findings suggest that meningococci are more susceptible to these drugs.

Gonococci. Gonococcal infections in mice have not proved satisfactory for chemotherapeutic studies of sulfonamide compounds. Virulent strains for mice are unknown, and in order to produce infections large doses of mucin-suspended organisms are required. The animals then often die as a result of the large endotoxic component rather than from the invasive element of the infection (Levaditi and Vaisman, 1937; Long and Bliss, 1938; Cohn, 1938). Sulfanilamide and certain of its derivatives have yielded rather disappointing results as chemotherapeutic agents in experimental gonococcal infections in mice.

Other Bacterial Infections. Buttle and associates (1937) observed that sulfanilamide protects mice against infections due to *B. typhosus* and *Paratyphoid B*, and occasionally cures mice of infections due to *B. aertrycke*. Experimental mouse infections with *Friedländer's bacillus* are not markedly influenced by sulfanilamide therapy, but sulfapyridine yields good results. Long and Bliss (1937) reported that sulfanilamide is strikingly beneficial in experimental *Cl. welchii* infections in mice. Sulfanilamide appears to modify favorably the course of *brucella* infection in guinea pigs (Welch and coworkers, 1938; Menefee and Poston, 1939). In experimental brucellosis in mice, Kolmer (1940) reported that sulfanilamide was therapeutically active against *Br. abortus*, considerably less effective against *Br. melitensis*, and inactive, as far as survival is concerned, against *Br. suis*. *Tuberculosis*, experimentally induced in guinea pigs, is not significantly affected by sulfanilamide, although some workers report a modification of the course of the disease.

Sulfanilamide is ineffective in *rabbit syphilis* and does not influence *S. pallida in vitro* (Campbell, 1937). The action of sulfanilamide with regard to *plasmodia* and *experimental malaria* is unsettled, although there are reports of curative effects, especially in monkeys (Coggeshall, 1940).

Virus Infections. In general, sulfanilamide and its congeners have not proved effective in preventing or curing experimental virus infections. Experimental *poliomyelitis* in monkeys and infections in mice due to *lymphocytic choriomeningitis* and *human encephalitis virus* do not respond to sulfanilamide therapy. Drugs in this category are of questionable value in the treatment of *dog distemper*, and certain compounds are moderately but not strikingly beneficial to mice infected with the *influenza virus*. *Lymphopathia venereum* infections in mice and guinea pigs are apparently benefited by certain sulfanilamide derivatives.

Mechanism of Action. Sulfanilamide and its congeners differ from all other antiseptics in that they represent the first chemotherapeutic agents capable of being taken orally which are not only highly effective against serious bacterial infections but which also exhibit very little toxicity for the host. The mechanism of action of these compounds has therefore received considerable attention. The importance of elucidating the mechanism of action lies in the fact that a more intelligent development of new compounds and a more rational use of sulfanilamide and its allied drugs will then be possible.

Numerous theories, many unsubstantiated by facts, have been advanced to explain the mechanism of antibacterial action of the sulfonamide chemicals. A problem of major importance is whether sulfanilamide acts directly on the bacteria or whether the defense forces of the host are involved. The consensus of opinion is that both factors cooperate. That the drug acts directly on bacteria is strongly suggested by its bacteriostatic effect *in vitro* and the correlation between its activity *in vitro* and *in vivo*. Considerable evidence also exists to indicate the importance of the humoral and cellular defensive mechanisms of the body for the therapeutic efficacy of sulfanilamide. It appears, then, that the drug produces bacteriostasis and allows the defensive forces of the body to cope with the infection. In discussing this problem, Long and Bliss (1939) state that ". . . it seems possible to conclude sulfanilamide does not arouse a specific response on the part of the host. The production of antibodies is not stimulated, and there is no direct action upon the phagocytic mechanism. On the other hand, there is considerable evidence that the drug does act upon the microorganism *in vitro* and *in vivo*. Most workers are of the opinion that this action takes the form of an inhibition of the growth of the bacteria which brings about a suppression of their invasive power, and which thereby permits the defense mechanism of the host to accomplish its function." A similar opinion is expressed by Marshall (1939) who concludes that in the light of present knowledge ". . . the first effect in the cure of an infected animal or man is a direct action of the drug on the parasite rather than a stimulation of defense mechanisms of the host. Such defense mechanisms may, however, operate as the final stage in the chemotherapeutic process." In essential agreement with this point of view are Gay and associates (1937, 1939), Domagk (1937), Levaditi (1938), Keefer and Rantz (1939), Kolmer (1940), and many others.

Direct bactericidal effects are probably not produced by concentrations of sulfanilamide reached in tissues with doses employed clinically. Indeed, recovery may often occur without complete eradication of the bacteria from an original focus. For example, Longcope (1938) and others have demonstrated that sulfanilamide may be given longer than a month and yet hemolytic streptococci may persist in infected tonsils, and the same is true of latent foci in certain other types of infection. Relapses after withdrawal of sulfanilamide are therefore explained by the fact that improvement was due to drug-induced bacteriostasis, but that the ultimate destruction of the microorganisms had not been accomplished by the defense mechanisms of the body, thus permitting reinvasion of the tissues by bacteria from a local focus upon withdrawal of medication.

In treatment of certain urinary tract infections, however, sulfanilamide may actually produce sterilization by a bactericidal action when the pH and concentration of drug are optimal (Helmholtz and Osterberg, 1937). This is chiefly due to the fact that in the urine concentrations of sulfanilamide are reached which are 10 to 20 times higher than those attained in the blood, but also to the fact that urine is a poor medium for bacterial growth. The combination of high concentrations of sulfanilamide and a poor environment results in the death of organisms in the urinary tract which are not susceptible to the drug in other tissues.

Effect of Sulfanilamide on Bacterial Toxins. There is no conclusive evidence that sulfanilamide and allied drugs neutralize preformed toxins or inhibit their formation. The action of sulfanilamide on a number of soluble exotoxins has been investigated by various experimental procedures without any suggestion of an antitoxic property. (*See* Rosenthal, 1937; Garrod, 1938; Dawson and Hobby, 1938; Huntington, 1938; Neter, 1938; Osgood and Powell, 1938; Gay and associates, 1939; King and coworkers, 1939; Newman, 1940.) There is some evidence, however, that sulfur-containing organic chemicals may inactivate certain endotoxins. Thus, Levaditi and coworkers (1937) found that a diphenylsulfoxide derivative may protect mice against the toxic effects of meningococcal extracts, and Carpenter and his associates (1938) observed that mice were saved from the lethal effects of gonococcal endotoxin by sulfanilamide. Further data are necessary concerning such actions on toxic products of bacteria, and what rôle, if any, they assume in the chemotherapeutic effects of the sulfonamide drugs.

Effect of Sulfanilamide on Defensive Forces of the Body. It was observed quite early in the study of sulfanilamide that leukocytes are essential for bactericidal as opposed to bacteriostatic effects of the drug. Experiments *in vitro* indicated that the presence of white blood cells in the culture medium allowed otherwise bacteriostatic concentrations of the drug to kill the organisms, and studies *in vivo* demonstrated that active phagocytosis characterized the sulfanilamide-initiated recovery from bacterial infections. Granulocytopenic mice, for example, were shown by Bliss and Long (1937) to die after infection with hemolytic streptococci despite intensive sulfanilamide therapy.

Most workers are now agreed that phagocytosis is essential for the sterilizing action of the drug in animal infections. However, whether the drug actually stimulates the white blood cells to ingest bacteria or whether it alters the microorganisms in such a manner as to facilitate phagocytosis is subject to controversy. Long and Bliss (1939) believe from their extensive experimental observations that the primary action is on bacteria, and many share this point of view. For example, by producing bacteriostasis in streptococcal infections, the formation of substances (leukocidin) inimical to phagocytes is checked and these cells are then better able to perform their task. Gay and Clark (1937) are of a similar opinion, and summarize their experiments on streptococcal empyemas in rabbits by stating, "In other words, sulfanilamide apparently produces bacteriostasis sufficiently marked to protect accumulated leukocytes and to allow the natural defense macrophages to accumulate. There is direct evidence that the drug does not in itself stimulate the mobilization of the macrophages. There is no evidence that the cell reaction which finally accounts for the disposal of the organisms is other than local." Subsequent *in vitro* investigations by Gay and coworkers (1939) on the mode of action of sulfanilamide on streptococci confirm this view.

Sulfanilamide does not enhance the bactericidal effect of human serum, and antibody formation is not promoted. For example, animals recovering from bacterial infections after sulfanilamide therapy may show no immunity upon reinfection. This does not signify that sulfanilamide interferes with antibody formation because the animals may recover from certain infections too quickly for natural immune processes to become operative.

In *summary,* it may be stated that the bacteriostatic action of sulfanilamide combines with the normal cellular and humoral defense mechanisms to account for the dramatic results seen in animal infections. Only the bacteriostatic factor is operative in experiments performed *in vitro* and hence the results obtained are far less impressive.

Morphological Changes Produced in Bacteria. Several investigators have observed morphological, capsular and growth changes in a variety of bacteria after contact with sulfanilamide *in vitro* or *in vivo*. Streptococci, for example, may show increased length of chains, swelling, staining alterations, etc. (Lockwood and Lynch, 1938). Meningococci may swell, become irregular or piriform in shape and manifest staining abnormalities. Evidently microorganisms showing these degenerative changes lose little or none of their virulence when transferred to a sulfanilamide-free environment.

Effects of Sulfanilamide on Bacterial Metabolism. The morphological changes produced in bacteria by sulfanilamide suggest that some basic alteration in growth and reproduction has occurred. Lockwood and Lynch (1938, 1940) investigated the influence of certain protein substrates upon the efficacy of sulfanilamide *in vitro,* and suggested that peptone and sulfanilamide may exert opposing effects. They believe that sulfanilamide may depress the specialized metabolic activity required of invasive organisms and prevent the utilization by bacteria of a native protein substrate essential for their growth. Fleming (1940) has also observed the antagonism between peptone and the bacteriostatic power of sulfanilamide. Levaditi and associates (1938, 1939) expressed a somewhat similar theory in that they believe sulfanilamide to be converted in the body to a substance which combines with the proteins available for bacterial nutrition, rendering them unfit for bacterial assimilation. Thus, in the case of pneumococcal infections, sulfanilamide is thought to render the internal medium unfavorable for the capsulogenetic multiplication of the pneumococci, thereby increasing their susceptibility to phagocytosis.

Barron and Jacobs (1937) found that sulfanilamide in a concentration of 0.2 per cent inhibited only slightly the oxidation of glucose by hemolytic streptococci and the oxidation of glucose and lactate by Friedländer's bacilli. Measurements of the effect of sulfanilamide on the oxygen consumption of bacteria (beta hemolytic streptococci, gonococci, meningococci, pneumococci, types I and III) were performed by Chu and Hastings (1938). Concentrations compatible with those attained in the tissues during therapy (0.0132 gram per cent) caused no change (except with meningococci), and ten times this concentration produced variable effects. Concentrations of 0.660 gram per cent invariably reduced oxygen consumption. The results were nonspecific, however, and rat tissues (liver, diaphragm, blood) were similarly affected.

Anti-Catalase Action of Sulfanilamide. The ability of sulfanilamide to inhibit catalase has been investigated by Locke, Main and Mellon (1938). These investigators proposed the theory that sulfanilamide is changed locally in infected foci to a catalase-inhibiting agent by the oxidative action of bacteria. As a result the hydrogen peroxide normally formed by bacteria (pneumococci and hemolytic streptococci) in the course of their metabolism and removed by the catalase present in blood and tissues accumulates and destroys the bacteria. Shinn, Main and Mellon (1939) and Locke and Mellon (1939) advanced evidence that the peroxide produced by bacteria converts sulfanilamide by oxidation to the hydroxylamine (p-hydroxylaminobenzene sulfonamide) which is responsible for the therapeutic effects (anti-catalase action). Further conversion to the p-nitroso benzene sulfonamide, in their opinion, may be the basis for the toxic effects of sulfanilamide.

In support of such a theory it may be stated that it would account for the unexplained *latent period* of several hours which is known to exist before the effects of sulfanilamide can be detected *in vitro.* The idea of an oxidation product of sulfanilamide being the effective antibacterial agent is not new and was suggested by Mayer (1937) who found that the hydroxylamine of sulfanilamide was very active *in vivo,* many times more potent *in vitro* than sulfanilamide, and that its action came on without a latent period.

Also acetylsulfanilamide is not readily oxidized to a hydroxylamine and this may explain its lack of therapeutic effect. In commenting on the anti-catalase theory, Long and Bliss (1939) point out that streptococci grow well in catalase-poor media and vary considerably in their ability to produce peroxide. In addition, there is no correlation between the property of peroxide production by bacteria and their susceptibility to sulfanilamide *in vitro* or their virulence for animals. Nevertheless, the theory of catalase inhibition is thought-provoking and deserves further study. The evidence for the anti-catalase theory has been well summarized by Mellon, Locke and Shinn (1940).

Oxidation Products of Sulfanilamide as the Effective Chemotherapeutic Agents. The investigations of Mayer on p-hydroxylaminobenzene sulfonamide as the chemotherapeutic oxidation product of sulfanilamide have been cited. Marshall and coworkers confirmed the high antibacterial potency of this oxidation product and its ability to act without a latent period, but they were unable to obtain definite evidence that the chemical was the agent responsible for the therapeutic actions of sulfanilamide (*see* Marshall, 1939; Bratton, White and Marshall, 1939).

Shaffer (1939, 1940) from existing data and from his own experiments, has further elaborated the theory that oxidation products of sulfanilamide and sulfapyridine are the effective antibacterial agents as well as the substances responsible for toxic effects, as follows: In the absence of atmospheric oxygen *in vitro* or in the tissues, sulfanilamide and sulfapyridine are without therapeutic effect, and this fact, coupled with the lag of several hours before the compounds inhibit bacterial growth, suggests that in themselves they are inactive. Active oxidizing agents, of sufficient oxidizing intensity, are highly bactericidal for many organisms, provided their action is not diverted from the bacteria by other reducing substances in the culture medium. Sulfanilamide, as shown by Fox, German and Janeway (1939), when added to aerobic cultures of hemolytic streptococci, allows a longer elevation of the electrode-potential than in control cultures, and the addition of cysteine, catalase or the exclusion of air not only lowers the potential of the cultures but reduces the bacteriostatic effectiveness of sulfanilamide. Warren, Street and Stokinger (1939) also noted that the addition of sulfanilamide to cultures of hemolytic streptococci was accompanied by an elevation of oxidation-reduction potential and that related compounds exerting no bacteriostatic action were without effect upon the culture potentials. Furthermore, Fox (1940) has reported that complete initial deprivation of oxygen interferes with bacteriostasis whereas increased oxygen availability magnifies the bacteriostatic action; that reducing agents and large inocula (which rapidly reduce the potential) obliterate bacteriostasis despite an excess of sulfanilamide; and that the use of a preformed oxidant derived from sulfanilamide, namely, parahydroxylaminobenzene sulfonamide, eliminates the usual initial growth period before bacteriostasis appears and gives a more prolonged action than sulfanilamide.

Shaffer refers to the anti-catalase action of oxidized sulfanilamide and the high *in vitro* potency of the hydroxylamine derivative. He noted in his own experiments that sulfanilamide and sulfapyridine are readily oxidized by a variety of chemical oxidizing agents as well as by electrolytic oxidation to characteristic cherry-red products which have an extremely high oxidizing intensity. The formation of such products *in vitro* by atmospheric oxygen is not possible but may be accomplished *in vivo* with the aid of various enzymes. The primary end-product seems to be nitroso-benzene sulfonamide. Evidence is cited to indicate that probably the reversible electrode couple is composed of the hydroxylamine and nitroso derivatives or the corresponding semi-quinone free radicals. When formed *in vivo,* such oxidation products would be hard to detect because they would rapidly lose their oxygen in destroying bacteria, in producing methemoglobin, and in reacting with the many reducing substances in tissues and tissue fluids. The oxidation products of sulfanilamide are promptly reduced by oxyhemoglobin and many cell constituents and metabolites.

The oxidant in the tissues capable of oxidizing sulfanilamide is unknown. Shaffer suggests that hydrogen peroxide, inert at low concentrations without catalysts, is a rapid oxidant of sulfanilamide when ferric or ferrous iron (of serum and tissues) is present, and that the peroxide accumulates locally due to inhibition of catalase by the products of the initial phase of oxidation of sulfanilamide. Once slowly started, more oxidation products toxic for bacteria would be formed in proportion to the availability of oxygen and the production of peroxide. The selective action of oxidized sulfanilamide on bacteria rather than on tissue cells of the host may possibly be explained by the lower oxygen tension of tissues (than blood), their higher metabolism and their higher catalase content. Thus Shaffer believes that sulfanilamide provides a mechanism by which the sterilizing oxidation intensity of molecular oxygen is applied nearly at its maximum to bacteria and unavoidably also to some extent to host tissues. Obviously the theory is too new to allow a statement as to its ultimate validity, but the supporting data are quite interesting and provocative.

Mechanism of Action of the Prontosils. That the prontosils are active by virtue of their release of sulfanilamide has already been discussed, but the evidence for this may now be summarized. The prontosils are inactive *in vitro,* and their change in the body to sulfanilamide is suggested by the appearance of the latter in the tissues and urine (Fuller, 1937; and others). Engel (1938), furthermore, demonstrated that prontosil can be reduced to sulfanilamide *in vitro* by liver, kidney and blood, and Spink and coworkers (1940) showed that various types of microörganisms could similarly change prontosil *in vitro.* Bliss and Long (1937) observed that the sera obtained from rabbits first injected with neoprontosil and later given a strong reducing agent (sodium formaldehyde sulfoxylate) intravenously, exhibited a bacteriostatic effect on hemolytic streptococci. They also found that cysteine hydrochloride reduced neoprontosil *in vitro* to a colorless solution which likewise possessed bacteriostatic properties. Finally, if the prontosil molecule is altered in such a way that it can no longer yield sulfanilamide upon reduction, the resulting compound is inactive. Most workers are agreed, therefore, that the prontosils owe the greater share, if not all, of their chemotherapeutic effect to sulfanilamide.

If this is true, it is reasonable to expect that the prontosils prove no more effective than sulfanilamide mol for mol. Several investigators, however, have claimed that the prontosils are as active as sulfanilamide, gram for gram, whereas sulfanilamide, a compound of lower molecular weight, should be the more potent on a weight basis. The criticism may properly be leveled at these experiments that the absolute dose of drug administered is not significant but rather that the level of sulfanilamide reached and maintained in the blood represents the only correct basis of comparison. Experiments designed to answer this problem, while not complete in all respects, do indicate that neoprontosil and sulfanilamide on a molecular basis are equally effective in the treatment of mice infected with hemolytic streptococci, and that on a weight basis neoprontosil is distinctly inferior to sulfanilamide (Feinstone, Bliss, Ott and Long, 1938). This strongly suggests that the prontosils are potent by virtue of their yield of sulfanilamide.

Pharmacological Actions. Sulfanilamide possesses no pharmacological actions which are of therapeutic benefit other than its effects on bacteria. Viewed in a strict sense, the drug is quite inert and large or toxic doses are needed to produce discernible effects on tissues and organs of the body. When tested on animals, sulfanilamide has no action in therapeutic doses on the heart, respiration, blood pressure, smooth muscles, uterus, renal function, parenchymatous organs, hemopoietic system, central nervous system and metabolic processes. The acute toxicity of the drug is low and the single oral dose representing the $L.D._{50}$ for animals is about 4.0 grams per kg (Marshall, 1939). When chronic medication is employed in animals, doses much larger than therapeutic may be administered without pathological changes or alterations in growth. Significant histological lesions in tissues occur only when large amounts are given.

It is true, however, that human beings manifest a number of untoward responses to therapeutic doses of sulfanilamide, some of which are not observed in animals. These are described in the chapter on clinical toxicity. Despite the fact that animals fail to show certain dangerous reactions to sulfanilamide observed in man, the results obtained from animal experimentation provide valuable information, especially in the preliminary testing of new compounds.

Absorption, Distribution, Fate and Excretion. *Absorption.* Sulfanilamide is poorly absorbed from the stomach but is readily absorbed from both the small and large intestines. This accounts for the more rapid absorption when the drug is given in solution, thus facilitating its passage into the duodenum. In man, absorption of a single oral dose is complete within three to five hours. The rapidity and completeness of intestinal absorption is indicated by the fact that, even in the presence of diarrhea, fecal excretion of sulfanilamide is negligible. Even in shock, sulfanilamide diffuses so rapidly that it is adequately absorbed once it is present in solution in the small intestine, as shown by Stead and Kunkel (1940) in a subject with postural hypotension and collapse induced by the upright posture. Sulfanilamide also readily enters the circulation after subcutaneous administration (Figure 89). By either route, a single dose produces a maximal serum concentration of sulfanilamide within two to four hours, after which the serum level falls rapidly due to excretion of the drug. These facts form the basis for the clinical practice of administering sulfanilamide at four-hour intervals in order to maintain a fairly constant blood level.

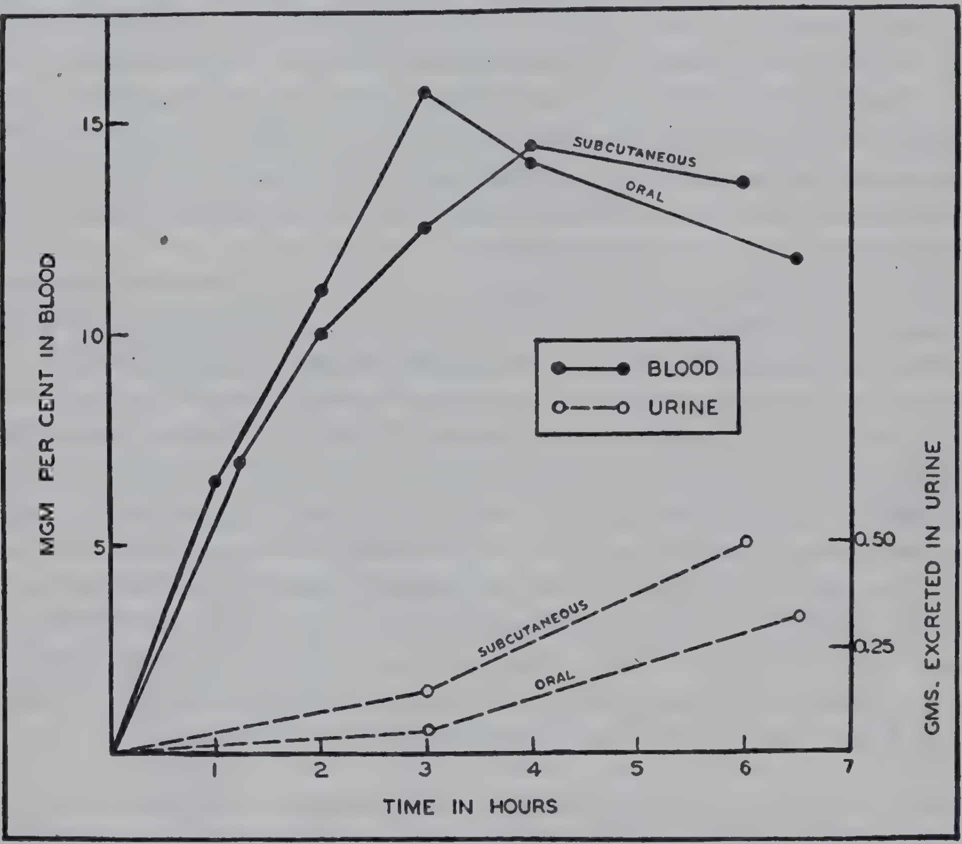


FIGURE 89. *Comparison of oral and subcutaneous administration of sulfanilamide in relation to blood levels and urinary excretion.*

Normal dog, given 0.1 gram per kg of sulfanilamide by mouth, and subcutaneously (1.25% solution). Note the rapid rise in the blood level of sulfanilamide after administration by either route and that subcutaneous injection of the drug does not lead to a higher blood concentration than when the compound is given by mouth; in fact, the curve of blood concentration is somewhat lower. Excretion of sulfanilamide in the urine, on the other hand, is slightly more rapid after subcutaneous than after oral administration. (After Marshall, Emerson and Cutting, 1937. Courtesy of *The Journal of the American Medical Association.*)

Distribution. Sulfanilamide is rapidly and uniformly distributed throughout all body fluids, an important factor in its value as a chemotherapeutic agent. It is distributed in a manner similar to urea (Marshall and associates, 1937), and has been employed as an experimental agent for the determination of total body water (Painter, 1938). Sulfanilamide and conjugated sulfanilamide have thus been identified in all normal and pathological fluids. The drug is found in transudates, edema fluid and exudates, in the spinal fluid, in cervical and prostatic secretions and menstrual blood, in saliva, gastric juice, pancreatic juice and bile, in the milk of lactating women, and in amniotic fluid and fetal blood and urine.

Fate. Sulfanilamide exists in the body fluids as such (free form) or as acetylsulfanilamide (conjugated form). Individuals vary considerably in the degree to which they conjugate sulfanilamide but, as a rule, from 10 to 20 (trace to 40) per cent of the drug exists in the body as the conjugated form (Marshall and associates, 1937; Stewart and collaborators, 1938). The ability to acetylate sulfanilamide varies with the species, dogs being incapable of this process whereas man and all other mammals examined thus far convert a considerable amount to the acetyl derivative. Conjugation of sulfanilamide apparently occurs in the liver (Stewart, Rourke, and Allen, 1939), and Klein and Harris (1938) have demonstrated that rabbit liver *in vitro* is capable of changing the drug to its acetylated form. The process is evidently reversible because after the administration of acetylsulfanilamide to animals, sulfanilamide can be found in small amounts in the blood, and the same is true in man (Ockerblad and Carlson, 1939).

The importance of conjugated sulfanilamide lies in the fact that it has no therapeutic effect in bacterial infections and yet may yield toxic derivatives, although it appears to be less readily oxidized than sulfanilamide. Inasmuch as free sulfanilamide is the active therapeutic agent and one cannot predict the blood level of the free form on the basis of the dose administered, due to varying degrees of acetylation and other factors, frequent estimations of the serum concentration of free sulfanilamide are essential when patients are being intensively treated with large doses for severe bacterial infections.

Excretion. Sulfanilamide is entirely eliminated from the body, the major part being excreted in the urine. Urinary excretion accounts for approximately 93 (89 to 98) per cent of the administered drug (Stewart and associates, 1938; and others). After administration of the drug ceases, sulfanilamide is rapidly eliminated from the body provided fluid intake is adequate and renal function is normal. Two to three days, however, may be required before all the sulfanilamide is eliminated after chronic medication is stopped (Figure 90). If renal function is poor, excretion is delayed and the drug accumulates in the body so that otherwise safe doses may readily result in toxic concentrations of the drug in the blood. Long and Bliss studied an anuric patient who was given a single dose of the drug, and found practically no variations in the blood concentration of sulfanilamide during an observation period of one week. A somewhat similar case occurring clinically has been reported by Bensley and Wilén (1939). Furthermore, the retained sulfanilamide may be progressively and almost entirely acetylated to the inactive form, as shown in nephrectomized rabbits by Stewart and coworkers (1939). The ability of patients to excrete sulfanilamide should be known before therapy is instituted and may be accurately predicted from the results of the phenolsulfonphthalein excretion test (Alyea and associates, 1939).

The *renal clearance* of sulfanilamide in dogs was found by Marshall and associates (1938) to be from 20 to 30 per cent of the simultaneously determined creatinine clearance, indicating reabsorption of 70 to 80 per cent of the drug reaching the tubules. The clearance rate was found to be independent of the plasma level but to be augmented by an increased rate of urine flow. In general, it may be stated that the mechanism for sulfanilamide excretion is much the same as that for urea, except that a greater proportion is reabsorbed by the tubules.

Stewart and his associates (1938), studying the renal excretion of sulfanilamide and acteylsulfanilamide in patients, confirmed these findings and noted that the rate of renal clearance of the conjugated product was greater than that of the free form (indicating less tubular reabsorption) and was independent of its concentration in the blood. They also emphasize the effect of water diuresis in hastening the excretion of sulfanilamide. Long and Bliss (1939) in particular have stressed the clinical importance of a water diuresis in hastening the elimination of sulfanilamide in patients manifesting acute toxic reactions, and have observed an hourly decrease in the blood concentration of the drug following the forcing of fluids. Conversely, fluids are restricted when it is desirable to maintain high levels of the drug in the body.

The *quantitative aspects* of the excretion of free and conjugated sulfanilamide in the urine have received the attention of a number of workers. Helmholtz and Osterberg (1937) found that patients on a restricted fluid intake who were given two grams of sulfanilamide daily excreted by the third day as much as 100 mgm of free and 90 mgm of conjugated sulfanilamide per 100 cc of urine. Long and Bliss have observed that in patients kept on a strict metabolic regimen the proportion of free sulfanilamide in the urine may vary from 25 to 75 per cent of the total amount of drug excreted. The relatively high urinary content of the

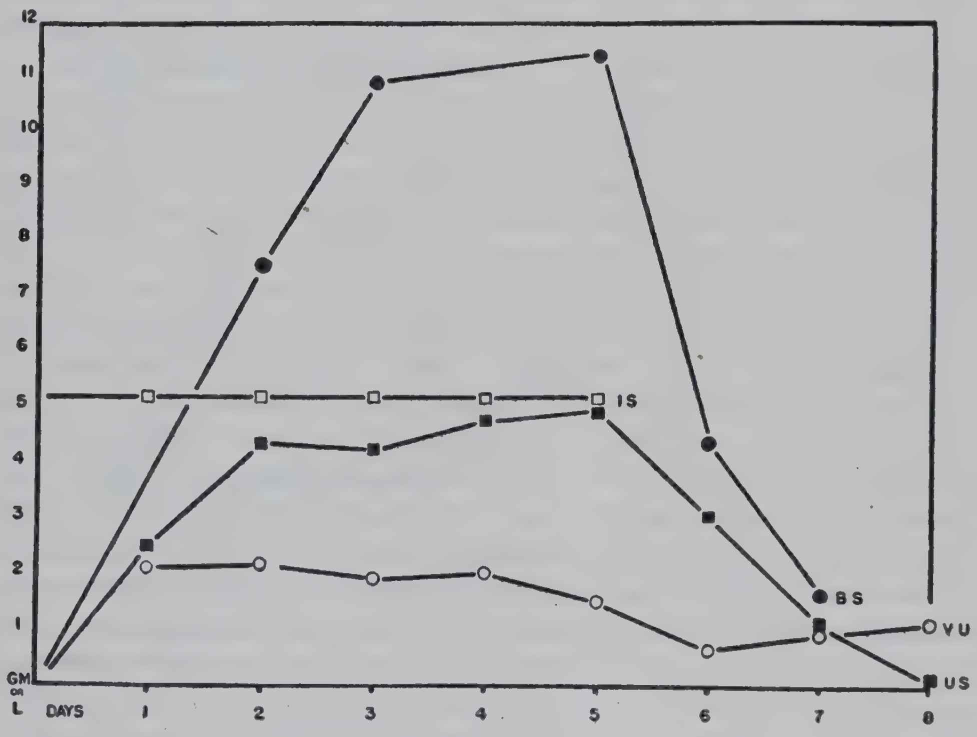


FIGURE 90. *Absorption, blood level and excretion of sulfanilamide in man.*

Open squares (*IS*) = intake of sulfanilamide; solid circles (*BS*) = blood sulfanilamide level; closed squares (*US*) = urine sulfanilamide level; open circles (*VU*) = volume of urine in 24 hours; abscissa, days; ordinate, grams or mgm% of sulfanilamide, or liters of urine. When five grams of sulfanilamide are taken orally each day, the blood level of sulfanilamide rises rapidly to reach a plateau of from 11 to 12 mgm% (total sulfanilamide) between the third and fourth days, due to equilibrium being established between intake and excretion. The amount of sulfanilamide excreted in the urine quickly rises to reach a maximum between the second and fourth days, at which time more than 90 per cent of the ingested drug appears in the urine. When sulfanilamide is stopped, the blood and urine levels fall rapidly during the subsequent two days. If the 24 hour urine volume is kept fairly constant by control of the diet and fluid intake, it is apparent how readily any given urinary concentration of sulfanilamide may be obtained. (After Stewart, Rourke and Allen, 1938. Courtesy of *The Journal of the American Medical Association.*)

acetylated form in comparison with its blood level is a direct result of the decreased renal tubular reabsorption of conjugated sulfanilamide. Inasmuch as more than 90 per cent of ingested sulfanilamide is excreted in the urine, it is obvious that with moderate water restriction one may obtain urinary levels of the drug from 10 to 20 times higher than those existing in the blood (Figure 90).

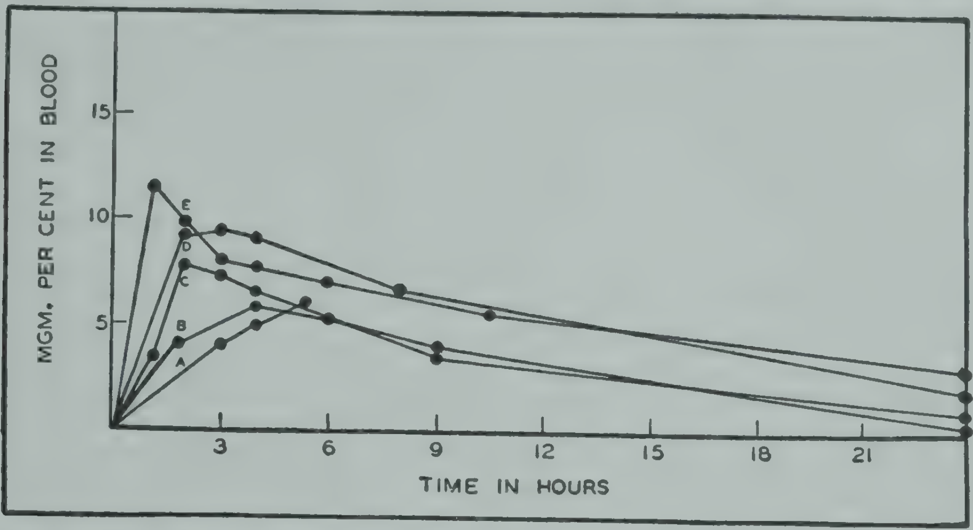


FIGURE 91. *Sulfanilamide concentrations in the blood of five patients following the oral ingestion of single large doses of sulfanilamide.*

A. 4.8 grams (0.09 gram per kg). *B*. 3.0 grams (0.05 gram per kg). *C*. 3.6 grams (0.05 gram per kg). *D*. 4.8 grams (0.066 gram per kg). *E*. 4.5 grams (0.06 gram per kg). Note that the peak concentrations vary considerably but are usually reached between the second and fourth hours. Variations are due mainly to differences in rates of absorption from the intestinal tract. The speed of decline in the blood concentration depends on the rate of urinary excretion. At the end of 24 hours, patients *D* and *E* still had appreciable amounts of the drug in the body, *D* having definite signs of renal impairment and *E* having just recovered from pneumonia. It is clear that blood concentrations of sulfanilamide depend on rapidity of intestinal absorption and urinary excretion of the drug and cannot accurately be predicted on the basis of the dose administered. (After Marshall, Emerson and Cutting, 1937. Courtesy of *The Journal of the American Medical Association.*)

These high levels are not only bacteriostatic but often bactericidal, and represent the basis for the therapeutic use of the sulfonamide drugs in certain infections of the urinary tract. The conjugated sulfanilamide is much less soluble than the free form and may precipitate out of the urine at room temperature.

Excretion of sulfanilamide also occurs in the *prostatic fluid,* a matter of importance in the therapy of infections of the prostate and posterior urethra. The concentration varies between 15 and 35 mgm per cent when full therapeutic doses are given, and the larger fraction of the drug is in the free form. *Fecal excretion* is negligible. Sulfanilamide also escapes from the body in the *milk,* which may contain up to 1.5 per cent of the total amount ingested. Human breast milk contains both free and acetylsulfanilamide. The concentration in milk is equal to or greater than the concentration present in the blood, but breast-fed infants do not obtain sufficient drug by this channel to be of therapeutic or toxic consequence (Adair and coworkers, 1938; Stewart and Pratt, 1938; Pinto, 1938; Foster, 1939). Sulfanilamide is also excreted in the *saliva* and *sweat.* It has likewise been identified in the *bile, pancreatic juice, gastric secretion* and *intestinal fluids* (Carryer and Ivy, 1939).

Blood and Spinal Fluid Levels of Sulfanilamide. The level of sulfanilamide in the blood, spinal fluid and other body tissues is a matter of utmost importance in therapy and has therefore received considerable attention. The blood level of sulfanilamide necessary for optimal therapeutic results in severe infections is between 10 to 15 mgm per cent; for moderately severe infections, blood concentrations of from seven to 10 mgm per cent are often effective; for mild infections, four to seven mgm per cent. Occasionally, concentrations of 15 mgm per cent or over may be desired for a short period of time, but the possibility of toxic reactions is thereby increased. When a single oral or subcutaneous dose of sulfanilamide is administered to patients, the maximal blood concentration is reached in from two to four hours, after which time the level falls rapidly until at the end of 16 to 20 hours little drug is left in the blood. The height of the blood level reached depends upon the dose given, variations in gastric emptying time and the speed of renal elimination, and varies considerably from patient to patient (Figure 91). With continued administration of regularly spaced constant doses, an equilibrium is reached within two to four days between the intake and excretion of drug, and when medication is stopped the blood level falls over a period of two days (Figure 90) (Marshall and associates, 1937; Stewart and coworkers, 1938). It has already been stated that from 10 to 20 per cent of the blood sulfanilamide exists in the conjugated form.

Fetal blood as well as amniotic fluid contains sulfanilamide and the concentrations of free and conjugated sulfanilamide in fetal blood are comparable to those present in the blood of the mother. Equilibration between fetal and maternal bloods occurs within five hours or less (Lee and associates, 1938; Speert, 1938; Barker, 1938; Adair and associates, 1938).

Sulfanilamide rapidly enters the cerebrospinal fluid, a matter of great importance in the therapy of meningitis. In spinal fluid, the concentration of the drug is approximately 25 per cent below the simultaneously determined blood level (Figure 92). Transudates and exudates of all descriptions have also been found to contain sulfanilamide, the concentration usually being from 10 to 25 per cent lower than that of the blood. Edema fluid, collected by means of Southey tubes employed in a case of intractable pitting edema of the lower extremities, was found to contain exactly the same concentration of sulfanilamide as the blood (Beck, 1939).

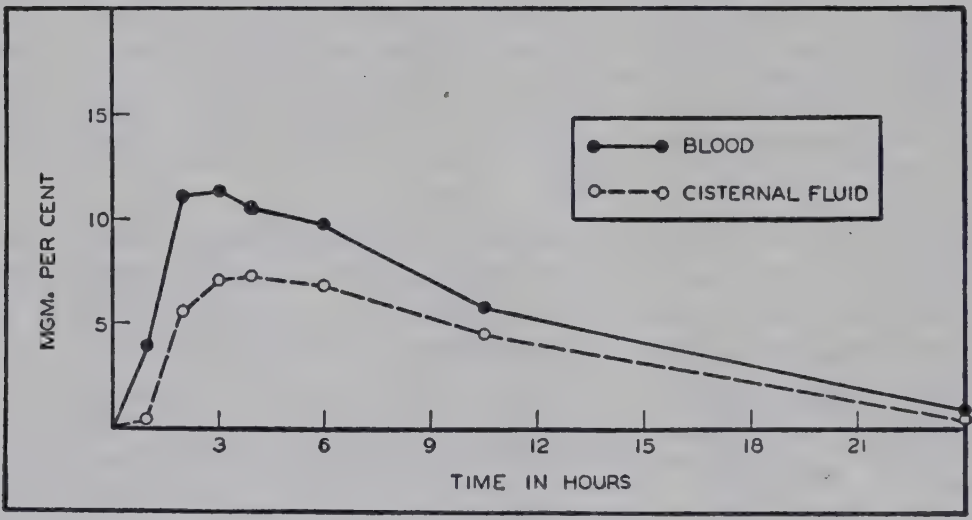


Figure 92. *Comparison of concentrations of sulfanilamide in the blood and cisternal fluid.*

Dog, given 0.1 gram per kg of sulfanilamide by mouth. The concentration of drug in the blood rises more rapidly than that in the cisternal fluid, but peak concentrations in both fluids are reached about the third hour. The concentration in the cerebrospinal fluid is approximately thirty per cent lower than that in the blood. (After Marshall, Emerson and Cutting, 1937. Courtesy of *The Journal of the American Medical Association.*)

Laboratory Determination of Free and Total Sulfanilamide. It has been emphasized that the determination of the sulfanilamide level in the blood is an important procedure in the therapeutic use of the drug. The method devised by Marshall and his associates (1937) and later modified by them (Bratton and Marshall, 1939) is satisfactory, sufficiently simple to be performed in a clinical laboratory or in the physician's office, and widely employed in the United States. It depends upon the diazotization of sulfanilamide in an acid solution and the subsequent coupling of the diazotized compound to make a dye, the color of which can be measured in a colorimeter against known standards. Marshall's method is as follows:

Reagents

1. A solution of trichloroacetic acid containing 15 grams dissolved in water and diluted to 100 cc.
2. A 0.1 per cent solution of sodium nitrite.
3. An aqueous solution of N (1-naphthyl) ethylenediamine dihydrochloride containing 100 mgms per 100 cc. This solution should be kept in a dark colored bottle.
4. A solution of saponin containing 0.5 gram per liter.
5. 4 N hydrochloric acid.
6. A solution of ammonium sulfamate, containing 0.5 gram per 100 cc.
7. A stock solution of sulfanilamide in water containing 200 mgms per liter. A weighed quantity of crystalline sulfanilamide is dissolved in hot water and diluted to appropriate volume. This solution can be kept for several months in the ice box. From the stock solution, standards for use are prepared. The most convenient ones are 1.0, 0.5 and 0.2 mgms per cent. To prepare these 5, 2.5 and 1 cc of the stock solution plus 18 cc of the 15 per cent solution of trichloroacetic acid are diluted to 100 cc.

Procedure for Blood

Two cc of oxalated blood are measured into a flask and diluted with 30 cc of saponin solution, and after 1 or 2 minutes precipitated with 8 cc of the solution of trichloroacetic acid. The free sulfanilamide is determined in the filtrate as follows: One cc of the sodium nitrite solution is added to 10 cc of the filtrate. After 3 minutes standing, 1 cc of the sulfamate solution is added, and after 2 minutes standing 1 cc of the solution N (1-naphthyl) ethylenediamine dihydrochloride is added. The unknown is compared with an appropriate standard which has been treated as above. To determine the total sulfanilamide, 10 cc of the filtrate are treated with 0.5 cc of 4 N hydrochloric acid, heated in a boiling water bath for one hour, cooled and the volume adjusted to 10 cc. The subsequent procedure is as above.

Procedure for Urine

The urine is diluted to contain about 1 to 2 mgms per cent of sulfanilamide and 50 cc of the diluted urine plus 5 cc of the 4 N hydrochloric acid are diluted to 100 cc. Ten cc of this second dilution are treated as a blood filtrate for free, and 10 cc heated without further addition of acid for total sulfanilamide. If the urine contains protein, it is diluted and treated as in the procedure for blood.

Comment

If blood values of 5 mgms per cent or less are expected, a 1:10 dilution of blood can be used. A 1:50 or 1:100 dilution of blood is convenient when using a photoelectric colorimeter. Sulfapyridine can be determined by this method. With blood levels above 5 mgms per cent, a correction of ten per cent should be added when a 1:20 blood dilution is employed. With values below 5 mgms per cent, no correction is needed. When dilutions of blood of 1:50 or 1:100 are employed, the recovery is quantitative.

Preparations. *Sulfanilamide,* U.S.P. XI (Second Supplement, 1939), is the official preparation. Its formula and the trade names under which it is marketed are given in Table 52. Preference should be given to the official name and preparation. Sulfanilamide is a white, odorless and slightly bitter, crystalline powder, soluble in water to the extent of 1:125 (0.8 per cent) at 25 C. to give a solution which is neutral to litmus. The drug is marketed in powder form for the preparation of solutions and in 0.3 and 0.5 gram tablets for oral use. The distribution and sale of sulfanilamide are regulated by the Federal Food and Drug Administration.

Benzyl sulfanilamide, sulfanilyl sulfanilamide and *sulfanilyl dimethylsulfanilamide* are not yet available for general use and have not been accepted by the Council. It is strongly recommended that the physician employ only those sulfanilamide derivatives which become official or which are found acceptable by the Council for inclusion in N.N.R.

Prontosil. This is an unofficial drug and is not accepted by the Council. No exact chemical standards of purity have been established for it. The formula for prontosil and its trade names are given in Table 52. The drug consists of a red powder, soluble in water to the extent of only 1:400 (0.25 per cent). The therapeutic use of prontosil has been discontinued in the United States.

Neoprontosil. This is also an unofficial drug for which exact chemical standards of purity have not been established. Its formula and trade names are given in Table 52. Neoprontosil is a red powder, soluble in water to the extent of about 1:25, and marketed in tablets for oral use and in sterile solution (2.5 per cent) for parenteral injection. The use of sulfanilamide has largely displaced the employment of neoprontosil in the United States.

Routes of Administration. *Oral.* Whenever possible, sulfanilamide should be administered by the oral route. This is the cheapest, easiest and safest method of giving the drug. Rapid absorption occurs and satisfactory blood levels may be readily reached and easily maintained by the use of properly selected and spaced doses of the drug by mouth. Sulfanilamide may be ingested in the form of tablets or capsules. If the tablets are pulverized and given in half a glass of water, absorption is considerably facilitated. The drug can be given in the formula of infants and to older children in jelly or cereal.

Subcutaneous Administration. The absorption of sulfanilamide is no more rapid from the subcutaneous tissues than from the intestinal tract (Figure 89), and subcutaneous injection of the drug offers no advantages except in patients who may be unable to take medication orally because of vomiting, coma or uncooperativeness, or in whom a satisfactory blood concentration has not been obtained by use of the oral route. Infants who are very ill should be given sulfanilamide by injection.

Definite disadvantages attend the subcutaneous injection of sulfanilamide, for example, expense, pain, and the difficulty of maintaining a constant blood level of the drug, especially when infusions are given every six or eight hours. Oral therapy should therefore be instituted or resumed as soon as possible. Indeed, it may be possible to circumvent the use of subcutaneous infusion by employing a *nasal tube,* the tablets being powdered and suspended in several ounces of water.

The preparation of a sterile solution of sulfanilamide for subcutaneous administration is as follows: A 0.9 per cent solution of sodium chloride is sterilized by boiling in a pyrex flask for several minutes. The solution is permitted to cool until bubbling has ceased and then 1.0 gram of sulfanilamide powder (not tablets) is added for each 100 cc (1.0 per cent solution), the flask being gently shaken until all the drug is dissolved. When the solution has cooled to 37 C. it is ready to inject. The technic is that for any hypodermoclysis, injection being made from an infusion bottle under the pressure of gravity. Enough sulfanilamide solution should be made at one time to last the patient for 24 hours, and it should be freshly prepared each day. It should be kept at room temperature to prevent the precipitation of sulfanilamide out of solution. Sterilization of the solution may be performed by boiling for five minutes or by autoclaving for five minutes at 10 pounds pressure. Solutions which have a slight yellow discoloration are decomposed and must not be employed.

Intrathecal Injection. In streptococcal, meningococcal and pneumococcal meningitis, sulfanilamide has been injected intrathecally as an adjuvant to, but not as a substitute for, oral or subcutaneous therapy. Whether this mode of administration is of value is questionable. After oral ingestion, sulfanilamide rapidly enters the cerebrospinal fluid where it reaches a concentration only slightly below that of the blood (Figure 92). When the drug is introduced into the subarachnoid space, the high local concentrations briefly obtained (10 to 16 mgm per cent) after a single injection of 80 mgm (Neter and coworkers, 1939) fall quickly because of the direction of the diffusion gradient.

Should intrathecal administration be performed, the solution used is sulfanilamide in sodium chloride solution, as previously described. The technic is that used for antisera. After spinal drainage, an amount of sulfanilamide solution (generally 10 to 30 cc) which is five to 10 cc less than the volume of spinal fluid removed is allowed to flow in by gravity, positive pressure being strictly avoided. Treatment may be repeated at eight hour intervals. Meningeal irritation does not result from the drug.

Other Routes of Administration. Intravenous injection of sulfanilamide is unnecessary and strictly contraindicated. Little quantitative information is available concerning the *rectal administration* of sulfanilamide but satisfactory therapeutic results have been obtained from retention enemas of the drug (Turell and coworkers, 1939). Absorption of sulfanilamide from the large bowel is considerably slower than from the small intestine. For example, Stead and Kunkel (1940) found that 300 cc of a one per cent solution of sulfanilamide instilled into the duodenum of human subjects allowed a blood level of six to eight mgm per cent of the free form to appear within 10 to 13 minutes, whereas blood levels of 2.4 to four mgm per cent were attained after one and one-half hours when the same amount of sulfanilamide solution was placed in the colon. The *topical application* of sulfanilamide is usually without effect, and the intrapleural or intraperitoneal injection of its solutions is not known to be of value so far as direct local action is concerned. However, evidence is accumulating to suggest that sulfanilamide applied locally may be beneficial in the treatment of infected surface wounds and in compound fractures.

Dosage. The dose of sulfanilamide cannot be stated categorically. It depends upon many factors, including especially the patient's age, the type and severity of infection, the route of administration, the functional capacity of the kidneys and the success with which the desired level of blood sulfanilamide is attained. Thus, children and young adults tolerate sulfanilamide better than do older individuals; severe infections necessitate heavier medication than mild ones; larger amounts of the drug must be given when the subcutaneous route is employed than when oral administration is used; great care must be exercised re-

TABLE 53

THE AMOUNTS OF SULFANILAMIDE NECESSARY TO ESTABLISH EFFECTIVE BLOOD LEVELS (10 TO 15 MILLIGRAMS PER CENT) QUICKLY IN PATIENTS ILL WITH SEVERE HEMOLYTIC STREPTOCOCCAL, MENINGOCOCCAL, GONOCOCCAL, PNEUMOCOCCAL OR WELCH BACILLARY INFECTIONS

(After Long and Bliss, 1939.)

Wt. of Patient	Initial Dose by Mouth	Maintenance Dose by Mouth Every Four Hours (Day and Night)	Dose Given in First 24 Hours	
Kg	Grams	Grams	Grams per Kg	Total
70	4.8	1.2	0.15	10.5
60	4.2	0.9	0.15	9.0
45	3.6	0.9	0.18	8.1
35	3.6	0.9	0.23	8.0
23	3.0	0.6	0.26	6.0
11	1.8	0.3	0.3	3.3

garding dosage in persons with impaired renal function; if satisfactory blood levels of sulfanilamide are not obtained with the usual doses, still larger amounts may be required or parenteral administration may be necessary. The best method of regulating dosage and placing sulfanilamide therapy on a safe and rational basis is to utilize the information obtainable from fairly frequent determinations of the sulfanilamide level of the blood. Such determinations are particularly desirable in treating severely ill patients with large doses of sulfanilamide.

Table 54

THE AMOUNTS OF SULFANILAMIDE NECESSARY TO ESTABLISH EFFECTIVE BLOOD LEVELS (4 TO 8 MILLIGRAMS PER CENT) IN PATIENTS ILL WITH MILD OR MODERATELY SEVERE TISSUE INFECTIONS IN WHICH SULFANILAMIDE THERAPY IS INDICATED

(After Long and Bliss, 1939.)

Wt. of Patient	Calculated Daily Dose		Dose by Mouth Every Four Hours (Day and Night)
Kg	Grams	Grams per Kg	Grams
70	5.4	0.08 –	0.9
60	5.4	0.09	0.9
45	5.4	0.12	0.9
35	4.2	0.12	1 of 1.2 * 5 of 0.6
23	3.6	0.16	0.6
11	1.8	0.16	0.3

* 1 dose of 1.2 grams followed by 5 of 0.6 gram each.

Oral. In *severely ill patients,* it is desirable quickly to establish blood levels of sulfanilamide of from 10 to 15 mgm per cent. The amounts of drug by mouth usually required for this purpose in patients of different weights are shown in Table 53, compiled by Long and Bliss (1939). It will be noted that a large initial dose is employed. This is followed by a maintenance dose given at four-hour intervals day and night in order to insure an even and constant blood level of the drug which is essential for best therapeutic results. Subsequent therapy depends on the course of the disease. If the desired concentration of sulfanilamide in the blood is not reached by the doses suggested in the table, larger amounts are given. The maintenance four-hour schedule is usually continued in severe infections until the temperature has returned to normal and remained there for at least three or four days. The dose may then be reduced by one-quarter to one-third and continued at this level for three or more days, and further reductions are made as convalescence continues. Finally, medication may be given only three or four times daily. The incidence of recurrences is decreased if small amounts of sulfanilamide are given until the patient is completely well. Treatment should be extended particularly in cases of bone infections or draining infected wounds or abscesses, and not discontinued until a week or longer after complete recovery has taken place.

In *moderately or mildly ill patients,* the initial large doses of drug employed in severe infections are not indicated, and the dosage scheme outlined in Table 54, compiled by Long and Bliss (1939), may be used as a basis for initiating therapy and obtaining blood levels of from four to eight mgm per cent. As a rule, these doses will be sufficient to arrest the infection, but they must be quickly increased if the disease is not readily brought under control. After the temperature has been normal for one or two days, the amount of drug administered may be reduced by approximately one-third, and as convalescence progresses concomitant reductions in the number and size of the doses are made.

Subcutaneous. This route, as stated previously, is employed only in severely ill patients in whom oral therapy is impossible. The doses given are larger than those used by mouth. Those recommended by Long and Bliss (1939) are as follows: The initial dose should be one-half the total amount given during the first 24 hours when the oral route is used (Table 53). Thus, for a 60 kg patient requiring 9.0 grams by mouth during the first day, the initial injection would contain 4.5 grams (450 cc of a 1.0 per cent sulfanilamide solution). Further injections are made at eight-hour intervals and each should contain one-third the total amount estimated for the first day of oral therapy. This dosage scheme results in a total daily dose of parenterally administered sulfanilamide which is one-sixth larger than would be given by mouth. The technic and disadvantages of this route have been described and oral therapy should be instituted as soon as feasible.

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CHAPTER 57

SULFANILAMIDE AND RELATED SULFONAMIDE DRUGS

II. THE CLINICAL TOXICOLOGY OF SULFANILAMIDE

Therapeutic doses of sulfanilamide produce a wide variety of toxic reactions in man, most of which are mild and inconsequential but a few of which are serious and occasionally fatal. It is important to recognize these toxic responses and to differentiate them from the illness for which sulfanilamide is being administered. The attention which has been given to the untoward effects of the drug, however, has caused many physicians to hesitate to use sulfanilamide even in cases where it is clearly indicated. This attitude is unfortunate because a knowledge of the toxic propensities of sulfanilamide, combined with the use of definite precautions which decrease considerably the possibility of a serious toxic reaction, enables the practitioner to administer the drug rationally and safely. Despite its wide employment, few fatalities have occurred which are directly attributable to sulfanilamide. The restriction of the lay use of sulfanilamide and the Federal control of its sale and distribution represent a commendable advance in the protection of the public.

Most patients receiving sulfanilamide experience mild toxic effects within the first 24 to 48 hours. These are particularly likely to occur if the patient is ambulatory. Children and young adults tolerate the drug better than do older individuals, debilitated patients or those with serious organic diseases. Approximately 10 per cent of patients may not be able to tolerate the drug. The more serious effects of sulfanilamide are related to the skin, bone marrow and blood. They occur as a result of the progression of milder toxic effects, excessive dosage or idiosyncrasy. In Table 55 are presented the frequency and importance of the untoward responses to sulfanilamide noted by Long and associates (1940) in an extensive experience with the use of the drug. Essentially similar findings have been reported in the statistical analysis by Brown and coworkers (1940).

Nervous System. A number of the milder symptoms noted after ingestion of sulfanilamide are referable to the toxic effects of the drug on the nervous system. Dizziness, tinnitus, malaise and headache are frequent. The patient may act as if he were slightly inebriated. Indeed, alcohol accentuates the symptoms so that its use should be interdicted during sulfanilamide therapy. The patient, if ambulatory, should be warned not to drive a car, pilot an airplane, etc. Headache is usually not significant but it may herald the onset of serious toxic effects. These symptoms do not interfere with therapy, are less noticeable if the patient is put to bed, and disappear readily upon cessation of medication.

Anorexia, nausea, vomiting and *diarrhea* are also commonly noted soon after full doses of sulfanilamide are administered, and may be sufficiently severe seriously to interfere with oral medication. They are due not to any local irritant

TABLE 55

THE CLINICAL TOXIC MANIFESTATIONS OF SULFANILAMIDE, SULFAPYRIDINE AND SULFATHIAZOLE WITH THEIR INCIDENCE AND TIME OF APPEARANCE [‡] [#]

TOXIC MANIFESTATION	SULFANILAMIDE	SULFAPYRIDINE	SULFATHIAZOLE
Nausea and vomiting	Fairly common, occurs early	Very frequent, occurs early	Uncommon
Dizziness	Common, occurs early	Common, occurs early	Uncommon
Psychoses [*]	0.6%, occur early	0.3%, occur early	Not reported as yet
Neuritis [†]	Very rare, generally early	Not reported	Not reported
Cyanosis	Very common, early and late	Faint, common, early and late	Uncommon
Acidosis [*]	1.9%, occurs at any time; (*see* discussion in text)	Not reported	Not reported
Fever [*]	10%, generally 5th to 9th day, may occur 1st to 30th day	4%, generally 5th to 9th day, may occur 1st to 30th day	10%, generally 5th to 9th day
Rash [*]	1.9%, may take any form, generally 5th to 9th day, may occur 1st to 30th day	2%, may take any form, 5th to 9th day, may occur 1st to 30th day	5%, nodular type common, may take any form, 5th to 9th day
Hepatitis [†]	0.6%, early or late	Not seen, but reported	Not reported
Leukopenia with granulocytopenia [†]	0.3%, early or late	0.6%, early or late	1.6%, early or late
Acute granulocytopenia [†]	0.1%, occurs 14th to 40th day, common 17th to 25th day	0.3%, occurs 14th to 40th day, common 17th to 25th day	Not reported
Mild hemolytic anemia	3%, early and late	Rare	Not reported
Acute hemolytic anemia [†]	1.8%, generally occurs 1st to 5th day	0.6%, generally occurs 1st to 5th day	Not reported
Hematuria [*]	Not reported	8%, generally early	2.5%, generally early
Anuria with azotemia [†]	Not reported	0.3%, generally 1st 10 days	0.7%, generally 1st 10 days
Hyperleukocytosis [*]	Generally in presence of acute hemolytic anemia	Generally in presence of acute hemolytic anemia	Not reported
Injection of scleras and conjunctivas [*]	Not reported	Not reported	4%, may occur with rash and fever, 5th to 9th day
Purpura hemorrhagica [†]	Not seen, but reported	Not seen, but reported	Not reported
Ocular and auditory disturbances [*]	Rare	Rare	Not reported
Jaundice [†]	With acute hemolytic anemia or hepatitis	With acute hemolytic anemia or hepatitis	Not reported
Painful joints [*]	Reported	Not reported	Reported with rash, etc.
Stomatitis [*]	Rare	Not reported	Not reported
Gastro-intestinal tract disturbances [*]	Bleeding rare, diarrhea uncommon	Rare	Not reported

[‡] After Long, Haviland, Edwards and Bliss, 1940.
[#] Hospitalized adults: 1000 treated with sulfanilamide; 297 treated with sulfapyridine; 271 treated with sulfathiazole.
[*] Best to stop drug and force fluids.
[†] Imperative to stop drug and force fluids.

effects of the drug on the gastro-intestinal tract but to a central action, as indicated by the fact that nausea and vomiting are noted after parenteral administration. Subcutaneous injection of the drug may be necessary in order to obtain blood concentrations sufficiently high to combat the infection. Fluid and electrolytes lost by vomiting and diarrhea should be replaced in order to prevent dehydration and acidosis. The symptoms enumerated are less marked if the patient is put to bed and they disappear readily when the drug is discontinued.

Mental symptoms of a mild nature are not uncommon after sulfanilamide. The appearance of mild intoxication similar to that produced by alcohol has already been mentioned. Depression, confusion and decreased mental acuity are not unusual, and rarely hallucinations, mania, delirium or stupor may occur. Toxic psychoses have been noted after the drug but may be due to an accentuation of the symptoms frequently accompanying severe febrile episodes.

Peripheral neuritis is rare after sulfanilamide. Ornsteen and Furst (1938) and Waugh (1939) record single instances of involvement of the lower extremities and Bucy (1937) described a case of toxic optic neuritis following sulfanilamide. Certain derivatives of sulfanilamide, however, are likely to cause a rather high incidence of peripheral neuritis which may be severe, protracted and crippling. The drugs particularly responsible for this complication are sulfanilyl sulfanilamide (*disulon*) and its dimethyl derivative (*uliron*) (Bannick and associates, 1938; Wigton and Johnson, 1938; Van Valkenberg and Borne, 1938; and many others).

Cyanosis. Some degree of cyanosis occurs in the majority (90 to 100 per cent) of patients receiving full doses of sulfanilamide. The incidence and intensity of cyanosis bear no close relationship to the dose, although in general the larger the amount of drug ingested the more likely cyanosis is to occur. The cyanosis varies in intensity and may be difficult to detect in those patients with dark skin color or when the hemoglobin value is low. It may appear within a few hours to a day or two after treatment is initiated, and disappears over a period of from one to three days when sulfanilamide is stopped. Dyspnea, which at times may be prominent, may occasionally accompany the cyanosis but it is rarely due to serious impairment of the oxygen carrying capacity of the blood. In fact, cyanosis is usually not harmful or alarming and dyspnea, if it occurs, is due to a primary toxic effect of the drug. The change in blood pigment which is the basis for the cyanosis is the subject of active dispute. Methemoglobin can be found in the blood of a large percentage of patients but whether this pigment can account for all cases of cyanosis or for all the color in any given case has been questioned. If sulfhemoglobin occurs, it is present in a negligible amount and does not account for the cyanosis.

Marshall and Walzl (1937) found only a slight decrease in the oxygen carrying capacity and failed to observe spectrographic evidence of methemoglobin in the blood of four of seven cyanotic patients who had received sulfanilamide. They therefore concluded that some other mechanism than the small amounts of methemoglobin probably present must account for the dark color of the blood, and suggested that a black oxidation product of sulfanilamide may be formed in the body and stain the red corpuscles without altering the oxygen carrying capacity of hemoglobin. The nature of the colored oxidation product could not be determined although *in vitro* Marshall and Walzl were able to form it from sulfanilamide by the use of certain oxidizing agents. Ottenberg and Fox (1938) noted that dilute solutions of sulfanilamide exposed to ultraviolet light turned first a strong violet and then a brownish color, and red blood cells added to such a solution immediately assumed the same chocolate brown hue shown by the blood of cyanotic sulfanilamide-treated patients. They suggested that cyanosis noted clinically may be due to a colored compound of sulfanilamide formed *in vivo* and similar to that produced by the action of ultraviolet light *in vitro*. Fox, Cline and Ottenberg (1939) reported further on the physicochemical characteristics of the ultraviolet irradiation product of sulfanilamide. Other investigators (Chesley, 1938; Posner and associates, 1938) confirmed Marshall and Walzl in being unable to account for the cyanosis on the basis of methemoglobinemia. James (1940) found that oxidation of sulfanilamide and sulfapyridine resulted in pigments which are absorbed by the lipoids of the red blood cell membrane and which alter the color of blood without affecting the oxygen carrying capacity or spectrum. He believes that this phenomenon may account for the cyanosis noted clinically when methemoglobin and sulfhemoglobin are absent.

The investigations of Wendel (1937), Wendel and associates (1939) and Hartmann and coworkers (1938), however, have shown that methemoglobin is the major abnormal blood pigment formed by sulfanilamide, and have established that methemoglobinemia is the most important cause of cyanosis in patients treated with sulfanilamide. Wendel tested the blood of several hundred patients on sulfanilamide therapy by means of a spectroscopic method which is claimed to be quite accurate and within the scope of clinical laboratories, and he found that methemoglobin was demonstrable in all specimens containing more than four mgm per cent of the drug. Concentrations of methemoglobin of 15 to 30 per cent and higher were noted. Wendel attributes the discordant results in the literature to the use of inadequate methods for the detection of small amounts of methemoglobin, requiring levels as high as 20 to 30 per cent as compared with levels as low as three per cent for his technic. This investigator was unable to detect the black pigment referred to in any of the bloods examined, but Wendel and coworkers (1939) confirmed the colored derivatives produced by irradiation of sulfanilamide and noted that they rapidly convert hemoglobin to methemoglobin. Hartmann and his collaborators, employing Wendel's method, were able to detect methemoglobin in the blood of every cyanotic sulfanilamide-treated patient whom they examined, and noted that cyanosis occurred in almost all persons receiving 0.1 gram or more of drug per kg during a 24 hour period. Large doses of sulfanilamide (0.15 to 0.2 gram per kg) often caused the appearance of characteristic cyanosis in from two to five hours, at which time the methemoglobin usually amounted to 10 per cent of the total blood pigment. Although no exact relationship between the degree of methemoglobinemia and the concentration of sulfanilamide in the blood was demonstrable, the disappearance of methemoglobin after withdrawal of the drug roughly paralleled the fall in blood level of sulfanilamide.

Others have corroborated the aforementioned findings that methemoglobin is responsible for the cyanosis. Harris and Michel (1939), in an extensive study of 476 patients receiving sulfanilamide, found methemoglobin in the blood of 277 (58 per cent) and sulfhemoglobin in the blood of 37 (7.8 per cent), and suggested that the drug is changed in the body to a substance capable of altering hemoglobin. Considerable evidence now exists that oxidation products of sulfanilamide can oxidize hemoglobin. Harris (1939) observed that sulfanilamide changes hemoglobin to methemoglobin after interacting with tissue *in vitro*. Rimington and Hemmings (1939) have advanced evidence to suggest that oxidation of sulfanilamide and certain allied drugs results in a substance (hydroxylamine derivative or o- or p-iminoquinone) capable of causing methemoglobin, porphyrin and coproporphyrin, the porphyrinuria noted by them possibly occurring from the degradation of methemoglobin. Still other workers have corroborated the importance of methemoglobin as the cause of the cyanosis (Vigness, Watson and Spink, 1940; Fox and Cline, 1940). Fox and Cline utilized the most delicate of all spectrographic methods, the recording spectrophotometer of Hardy, and demonstrated the presence of methemoglobin in the blood of patients receiving sulfanilamide. Some sulfhemoglobin was also observed.

At the suggestion of Wendel (1937), Hartmann and his coworkers employed methylene blue to prevent or abolish the sulfanilamide-induced methemoglobinemia and cyanosis by converting the oxidized pigment to ordinary hemoglobin. The rationale for this therapy is fully discussed under methylene blue (page 870) (Figure 87). In children, methylene blue may be given orally in a dose of 0.4 to 0.8 gram daily dependent on the patient's weight, and administered in six divided doses throughout the 24 hours. Hartmann and associates found this procedure effective in preventing the appearance of methemoglobinemia and cyanosis. When severe cyanosis is present in patients receiving sulfanilamide, it may be relieved within 30 minutes by the slow intravenous injection of methylene blue in a dose of 1.0 to 1.5 mgm per kg of body weight, given as a 1.0 per cent aqueous solution.

The investigators mentioned also found that the dye, given orally with sulfanilamide, neither prevents other toxic reactions to the latter drug nor interferes with its therapeutic efficacy. The necessity for relieving cyanosis arises especially when the methemoglobinemia is likely further to impair inadequate tissue oxygenation, as in patients with anemia, pneumonia, or cardiac failure, when cyanosis from causes other than sulfanilamide must be recognized (pneumonias), and when operative procedures requiring anesthesia are contemplated. A better evaluation of the progress of the case is also obtained by removal of the cyanosis which often makes the patient's condition appear deceptively alarming. Most cases of cyanosis, however, may be disregarded because the percentage of methemoglobin (10 to 12 per cent) is not injurious unless the patient is very ill. Methylene blue is apparently harmless, although it may sometimes cause nausea, vomiting or diarrhea after its oral use. When given intravenously, care must be exercised to prevent extravasation of the solution into the tissues. The clinical efficacy of methylene blue as outlined has been confirmed by a number of investigators (Wendel, 1938; Richardson, 1939; Campbell and Morgan, 1939; Vigness and coworkers, 1940).

Drug Fever. Fever may occur from sulfanilamide therapy and it is necessary to be able to differentiate drug-induced fever from that caused by the original infection or a recrudescence of it. Furthermore, hyperpyrexia due to sulfanilamide is one of the most important warning signs and calls for the cessation of medication. In a careful study of the phenomenon, Hageman and Blake (1937) noted that 21 (15.7 per cent) of 134 patients receiving sulfanilamide developed fever, and in nine cases there was an accompanying maculopapular rash. Mild eosinophilia was also observed in some patients. The febrile episode was characterized by an abrupt onset and usually appeared between the seventh and tenth day of drug therapy, although it occurred as early as the fourth and as late as the thirteenth day in a few instances. The fever sometimes appeared after the dose of sulfanilamide had already been decreased or after complete discontinuance of medication. Long and coworkers (1939, 1940) have had practically the same experience concerning drug fever as have Hageman and Blake. The incidence as reported by them is higher in adults (10 per cent in 1000 patients) than children, and the time of onset, although usually between the fifth and tenth day, sometimes occurred as early as two hours or as late as 21 days after starting sulfanilamide.

Accompanying the drug-induced fever there may be severe chills, malaise and headache. Tinnitus and nausea may also occur and itching and dermatitis may develop. The temperature occasionally reaches 106 F. and has been known to subside despite continuation of sulfanilamide therapy. This type of drug fever is similar to that seen in serum sickness, but demonstrable skin sensitivity to the drug is lacking and adenopathy, arthritis and serum precipitins are not present.

The differentiating feature in the diagnosis of the sulfanilamide-induced fever is that it usually occurs after the fever and constitutional symptoms due to the infection have been brought under control. The sudden development of a high temperature and chills after a period of improvement should be suspected of being due to sulfanilamide (Figure 93). The diagnosis can be firmly established by stopping sulfanilamide and forcing fluids, in which case defervescence occurs within 36 to 48 hours. When fever caused by sulfanilamide is superimposed upon that due to the infection, the diagnosis is more difficult but it will then be noted that the temperature suddenly rises higher than usual without the cause being apparent from the clinical course of the infection.

Medication should be discontinued when fever appears during the course of sulfanilamide therapy. Fever may also herald the onset of serious toxic reactions such as acute hemolytic anemia or agranulocytosis. If a second course of sulfanilamide is given at some time in the future, the patient is again likely to experience an acute febrile episode. Long and Bliss (1939) observed a number of such cases, and noted the rapid appearance of fever, chills, malaise, headache and occasion ally a peculiar erysipeloid lesion of the face, sometimes within an hour after the ingestion of 0.6 gram of sulfanilamide. Gallagher (1939) reported a similar instance. In order to avoid this complication, Long and Bliss suggest that a small test dose (0.3 gram) be given to patients with a history of sulfanilamide fever, and the temperature recorded frequently for a period of twelve hours. If a rise in temperature or untoward effects do not appear, it is generally safe to continue sulfanilamide therapy.

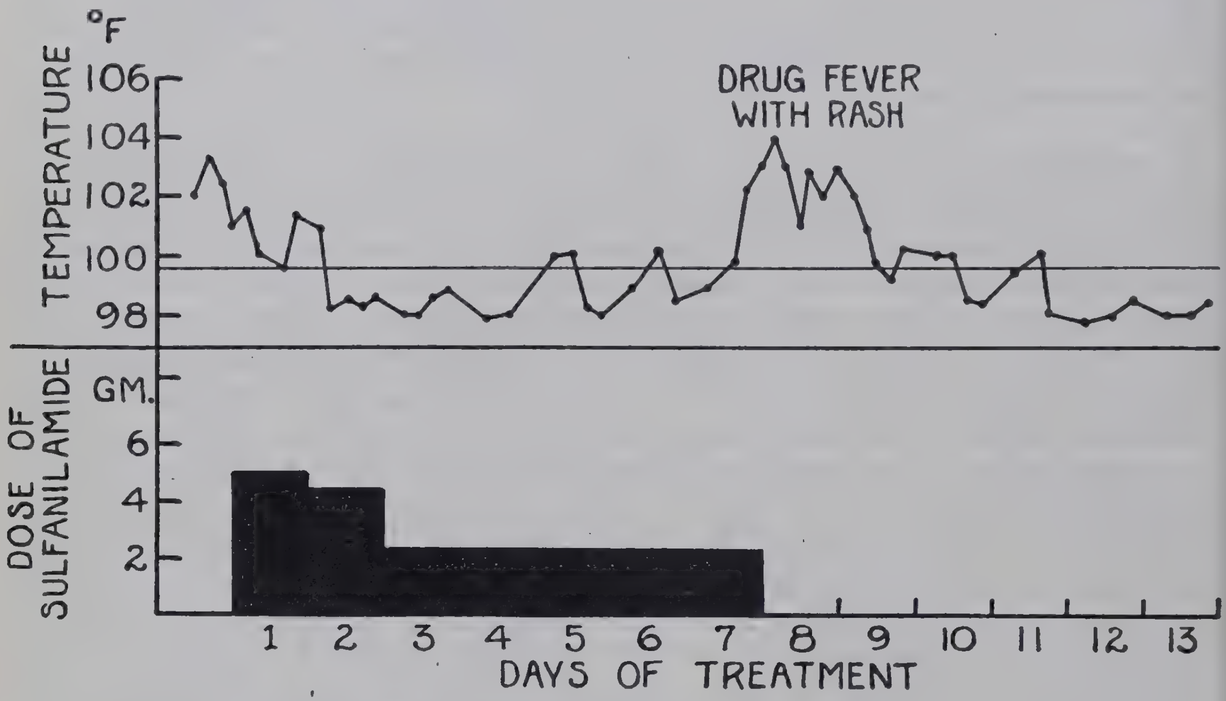

FIGURE 93. *Drug fever due to sulfanilamide.*

Male, aged 70, facial erysipelas and acute mastoiditis. Culture of the ear showed *beta* hemolytic streptococci. Sulfanilamide therapy caused a rapid disappearance of fever and symptoms. On the seventh day, however, the temperature rose sharply and a diffuse morbilliform rash appeared which quickly became hemorrhagic. Sulfanilamide was discontinued and the rash and fever subsided in three days. A diagnostic feature of drug fever due to sulfanilamide is the latent period of seven to ten days before it appears. (After Hageman and Blake, 1937. Courtesy of *The Journal of the American Medical Association.*)

Sulfanilamide Dermatitis. A variety of cutaneous eruptions occur from sulfanilamide therapy. These may be urticarial, angioneurotic edematous, erysipeloid, morbilliform, scarlatiniform, petechial and purpuric, and the lesions occasionally may progress to an exfoliating dermatitis. The rash ordinarily appears without prodromal warning and is usually accompanied by fever and malaise. Itching may or may not accompany the dermatitis. The time of onset is most frequently between the eighth and twelfth day, but the lesion may appear earlier or as late as the third week after sulfanilamide therapy is started. The eruption may be strictly localized or general in distribution, but most commonly it includes the face, trunk and extremities. Very rarely, the mucosae are involved. The dermatitis may be mild and brief in duration or severe and protracted. The lesions usually clear rapidly upon cessation of the drug and leave no residua, although desquamation may occur. Even if sulfanilamide is continued the dermatitis often fades and disappears completely within two or three days. The incidence of skin rashes reported by Hageman and Blake (1937) was six per cent of 134 patients; that by Long and associates (1940), somewhat lower (1.9 per cent of 1000 patients).

The relation of sulfanilamide dermatitis to exposure to sunlight or ultraviolet irradiation has occupied the attention of several investigators, and from both clinical and experimental studies it appears certain that in some cases, at least, a definite element of heliosensitivity is concerned in the production of the lesions (Frank, 1937; Newman and Sharlit, 1937; Brunsting, 1937). The work of Brunsting (1937) and Rimington (1938) indicates that the excretion of urinary porphyrins is increased during the period of the rash. The studies of Rimington and Hemmings (1939) on the effects of sulfanilamide on porphyrin metabolism have been cited.

Severe anaphylactic reactions occasionally with bronchial asthma may accompany urticarial or angioneurotic edematous lesions, but fortunately they are rare. Epinephrine may be required to control the symptoms. The blood shows no abnormalities as a result of sulfanilamide dermatitis, except occasionally an eosinophilia. Even when the lesions are essentially hemorrhagic in nature the platelets are normal, suggesting a primary vasculotoxic effect of the drug in this type of lesion. The most serious form of cutaneous eruption is an exfoliative dermatitis which may prove fatal. It may be associated with acute hepatitis or other serious manifestations of sulfanilamide toxicity.

The *diagnosis* of sulfanilamide dermatitis may be readily made, although the morbilliform rash may be difficult to distinguish from measles. *Treatment* other than expectant and symptomatic is unnecessary. It appears wisest to stop sulfanilamide when a cutaneous eruption appears, unless the patient's life depends on continuance of medication. Angioneurotic and widespread urticarial manifestations in particular require cessation of therapy. Resumption of the drug after fading of the dermatitis may be undertaken after a test dose of 0.3 gram has been given to discover the patient's sensitivity and provided no untoward response occurs within 24 hours. The readministration of sulfanilamide to a patient who has previously experienced drug rash or fever from it may quickly result in an erysipeloid eruption about the face (Long and Bliss, 1939). A scarlatiniform rash with fever and leukocytosis may occur in some individuals and increased capillary fragility and occasionally arthritis have been observed from continuance of medication (Schlesinger and Mitchell, 1938). Individuals receiving sulfanilamide should not be unduly exposed to the sun or to ultraviolet irradiation, and perhaps should avoid such exposure until three or four days after cessation of therapy.

Disturbance in Acid-base Equilibrium. Sulfanilamide in full clinical doses may cause mild to moderate disturbances in the acid-base equilibrium. These are rarely serious, are usually well compensated and do not constitute a reason for discontinuance of therapy. The nature of these changes is a matter of dispute, some claiming that a primary alkali-deficit type of compensated acidosis occurs and others that a primary CO_2-deficit type of compensated alkalosis is present.

Long and Bliss (1937) reported instances of clinical acidosis, and Southworth (1937), Strauss and Southworth (1938), Towsley and Engelfried (1938) and Beckman (1938) have apparently confirmed this finding in that they observed an increase in the pH of the urine due to the renal excretion of alkali (Na and K) accompanied by a decrease in the CO_2 combining power of the plasma after administration of the drug. The mechanism of the renal loss of fixed base has not been explained, but it has been suggested that sulfanilamide in some manner causes the renal tubules partially to lose their ability to reabsorb fixed base. Occasionally, the acidosis was uncompensated and definite hyperpnea developed. On the basis of these reports, Long and Bliss recommended the simultaneous administration of sodium bicarbonate (0.5 to 0.6 gram for adults) with each dose of sulfanilamide and this practice was at first widely adopted.

On the other hand, Hartmann, Perley and Barnett (1938) and Hartmann (1939) found in the patients they studied that, although the urine became alkaline, it did so as the result of renal compensation for a primary CO_2 deficit in the serum. In other words, a loss of serum carbon dioxide occurred, the alkalinity of the serum therefore rose, as shown by an elevation of pH, and the kidney excreted an alkaline urine in order to correct the disturbance. They believe that hyperventilation, observed in some patients, may be the cause of the loss of serum CO_2. If this explanation is correct, it is reminiscent of the dyspnea observed in salicylate poisoning. Hartmann and his coworkers are thus inclined to believe that a hyperventilation alkalosis occurs and they disapprove of the routine use of sodium bicarbonate which, in their opinion, may cause an uncompensated alkalosis under certain circumstances (*e.g.*, chloride depletion from prolonged vomiting). Furthermore, Hartmann (1939) gave ammonium chloride to a normal subject in order to produce an acid excess type of acidosis which was compensated for by complete tubular reabsorption of sodium bicarbonate. Sulfanilamide was then administered and excretion of an alkaline urine did not occur, indicating that the renal tubules are quite capable of reabsorbing sodium bicarbonate when changes in the acid-base balance of the body fluids demand such reabsorption.

The entire problem of the effects of sulfanilamide on the acid-base balance of the body was carefully restudied by Beckman and associates (1940). These investigators found that during a period of continued administration of sulfanilamide there occurred a large urinary loss of sodium accompanied by a smaller loss of potassium and no loss of chloride. The serum sodium concentration was reduced to the extent of four to five mEq per liter, corresponding closely with the reduction in plasma bicarbonate. The plasma concentration of chloride increased to the extent of five to six mEq per liter. These changes in acid-base excretion and electrolyte pattern of the plasma occurred rapidly (within one to three days) at the outset of the period of sulfanilamide medication, and were steadily maintained until the drug was discontinued, whereupon recovery was prompt. Breathing experiments were also conducted in subjects given a single large dose of sulfanilamide (13.3 grams). Observations on the change in pulmonary ventilation, alterations in serum electrolytes, and renal loss of fixed base showed that the loss of bicarbonate in the urine was an almost immediate event which was followed by a gradual development of increased respiratory minute volume. Beckman and associates concluded that the hyperpnea observed clinically during the course of sulfanilamide therapy may be regarded as a secondary event compensatory to a depletion of plasma bicarbonate caused by the loss of fixed base in the urine, and that sulfanilamide causes an alkali-deficit type of acidosis.

Regardless of the merits of the two opposing views—hyperventilation alkalosis and alkali-deficit acidosis—it may be stated that the acid-base disturbances observed during sulfanilamide medication and due to the drug *per se* are mild and require no special treatment other than making certain that there is an adequate intake of sodium chloride. When a proper intake of sodium chloride is assured, adequate renal function regulates the electrolyte pattern and the acid-base balance of the body. The routine use of alkali seems to be an added and unnecessary burden to a sick patient and also it neutralizes the gastric juice. If other factors are present which tend to disturb the acid-base balance such as diabetes mellitus, ketosis, vomiting, diarrhea, renal failure, pneumonia, etc., more rigid attention must be paid to the possibility that sulfanilamide may accentuate the disturbance and therapy other than sodium chloride may be needed. The measures then to be employed are outlined in the chapter on water, salts and ions.

Toxic Effects on Red Blood Cells. *Mild anemia* is not infrequent in patients receiving sulfanilamide, especially when medication is continued for several weeks. The anemia tends to be macrocytic and mildly hypochromic. The condition is not serious and offers no obstacle to therapy. If the hemoglobin drops to 50 or 60 per cent of its normal value and sulfanilamide must be continued, a blood transfusion may be necessary. Both the red cells and hemoglobin slowly and progressively decline, the reticulocytes rise and a mild urobilinuria may often be noted. The last two features indicate clearly that the anemia is due not to depression of the bone marrow but to accelerated destruction of erythrocytes and it is likely that the anemia is mildly hemolytic in character. The bone marrow reflects these changes and shows a moderate normoblastic hyperplasia. Cessation of medication results in rapid improvement in the blood picture.

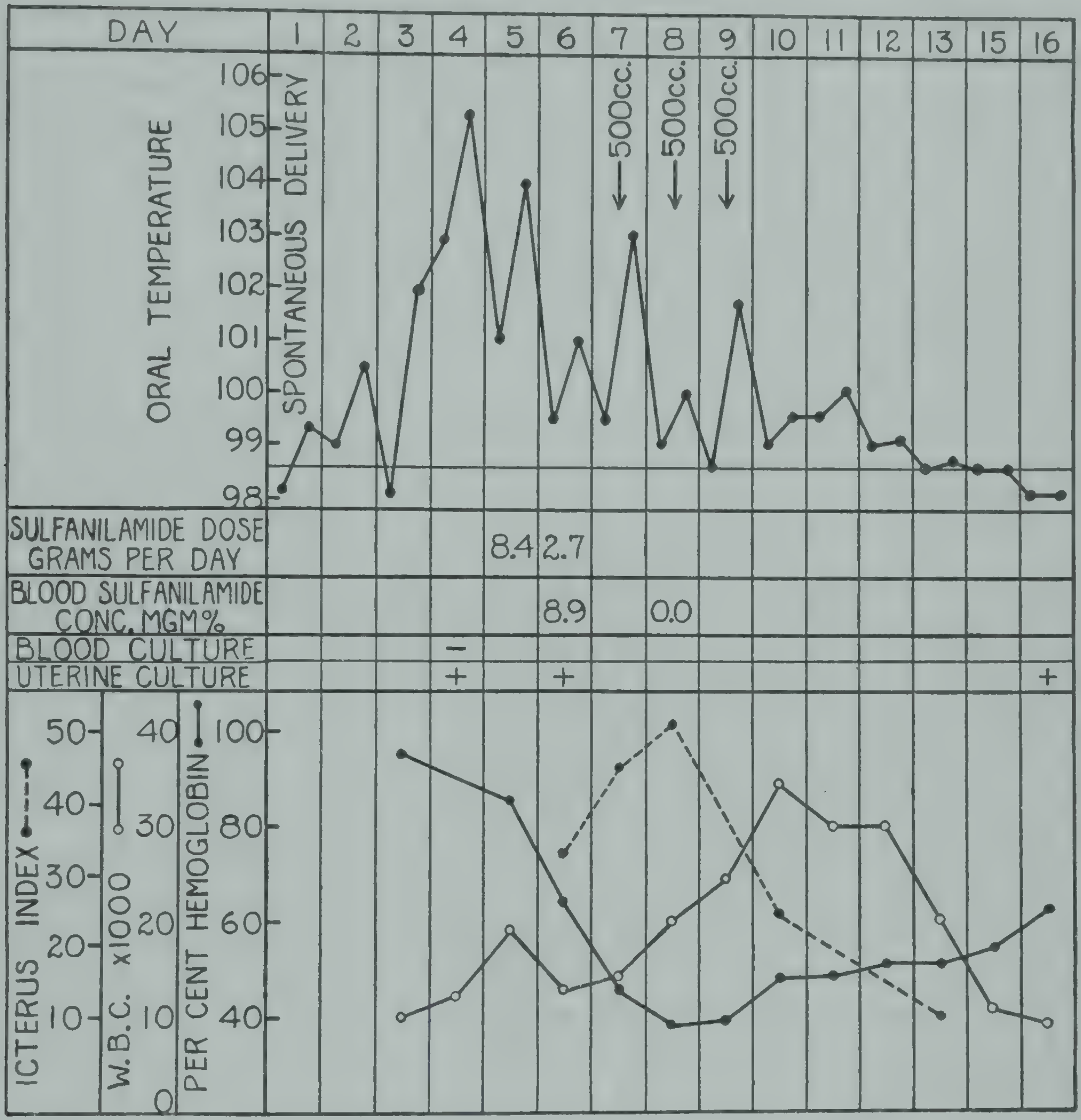

Figure 94. *Acute hemolytic anemia due to sulfanilamide.*

Female, aged 26. Forty-eight hours after a spontaneous delivery, the temperature started to climb. (Only the highest and lowest daily oral temperatures are shown in the chart.) An intrauterine culture taken on the fourth day, at which time post partum sepsis was definite, was positive for Group B *beta* hemolytic streptococcus, as was also true on the sixth day. Culture of the blood was negative. Sulfanilamide therapy was instituted on the fifth day, 8.4 grams being given orally during the first 24 hours and 2.7 grams during the subsequent eight hours. Within 24 hours after beginning of medication, the level of free sulfanilamide in the blood was 9.0 mgm per cent. The fever dropped precipitously and the patient improved greatly. However, acute hemolytic anemia quickly developed. The drug was immediately stopped and the blood level of the free fraction dropped rapidly to zero. The hemoglobin fell from 95 per cent (100 per cent = 14.5 grams) to 38 per cent. Observe that the hemolysis progressed even after the drug was discontinued and transfusion therapy initiated, indicating that the hemolytic combination had already occurred. Marked jaundice appeared and the icterus index rose to 51. The subsequent clinical course was uneventful. Note the marked leukocytosis (polymorphonuclear) which accompanied the initial phase of blood regeneration. Cervical culture on the 15th day showed the presence of the organism which persisted up to the time the patient was discharged. Sulfanilamide therapy would have been continued, despite the hemolytic anemia, if a more virulent organism had been identified. (From obstetrical service of Dr. N. J. Eastman, The Johns Hopkins Hospital; case data through courtesy of Dr. Joseph F. Sadusk, Jr., Yale University School of Medicine.)

Acute hemolytic anemia occurring suddenly during the course of sulfanilamide medication represents a real and serious danger, necessitates close observation of the patient and requires early recognition and treatment. The original report on this complication was by Harvey and Janeway (1937) who described three cases. The clinical picture does not differ essentially from that of other acute hemolytic anemias and the blood smear resembles in a striking manner that seen in acute phenylhydrazine anemia, reticulocytosis, normoblasts and marked variations in size and shape of the erythrocytes being prominent. The onset is sudden and the red blood cell count may fall by two or three million erythrocytes per cubic mm within a few hours to a day or two. Cyanosis, if present, is replaced by pallor. Nausea, vertigo, fever, leukocytosis, reticulocytosis, jaundice, hyperbilirubinemia, hepatic swelling, marked urobilinuria, and occasionally hemoglobinemia and hemoglobinuria comprise the essential clinical and laboratory features. A typical case is charted in Figure 94.

The *incidence* of the syndrome as reported by W. B. Wood (1938) who reviewed 21 cases observed at The Johns Hopkins Hospital was 8.3 per cent of 144 children and 2.4 per cent of 378 adults. The earliest signs of anemia appeared in from one to three days after the onset of sulfanilamide therapy, and maximal anemia occurred between the third and seventh day, nine of the 21 patients manifesting maximal anemia on the fifth day. No predisposing factors were discoverable and the hemolytic episode did not appear related to the dose of drug or its concentration in the blood. Fever, however, was observed in all patients at some time during the course of sulfanilamide. No fatalities occurred in the series cited and the two deaths in the subsequent 10 cases reported from the same hospital by Long and Bliss (1939) were not attributable to blood dyscrasia. Death, however, may result from this complication (H. Wood, 1938).

The *etiology* of the acute hemolytic anemia is unknown and acute hemolysis of red blood cells has not been produced *in vitro* or in experimental animals by sulfanilamide or its congeners. The anemia probably represents an idiosyncrasy. Patients once manifesting it are prone again to develop hemolytic anemia if given sulfanilamide subsequently. Five individuals of the 21 reported by W. B. Wood were subsequently given a second course of sulfanilamide and four again developed anemia.

Treatment consists of discontinuance of sulfanilamide, forcing of fluids and transfusions of blood repeated as often as necessary. Iron salts may be used to hasten blood regeneration. The hemolysis may continue for a time and the red blood cell count fall despite cessation of the drug and the use of transfusion, indicating that the hemolytic combination had already taken place. If there is indication of hemoglobinuria with resulting impairment of renal function, sufficient alkalis should be given to keep the urine alkaline for reasons explained elsewhere (page 246). If the infection for which sulfanilamide is being given is severe and dangerous to life, sulfanilamide may be continued despite the anemia provided it is possible to give repeated blood transfusions.

Measures designed to lessen the occurrence and severity of hemolytic anemia and to insure its early detection include daily determination of the patient's hemoglobin during the first week and biweekly thereafter, frequent examination of the urine for urobilin during the first week, thorough examination into the cause of every febrile reaction, careful questioning of the patient concerning premonitory symptoms, withdrawal of the drug at the first sign of a developing acute anemia and avoidance of the use of sulfanilamide (if possible) in persons who have previously experienced the disorder.

Toxic Effects on White Blood Cells. The possibility of agranulocytosis occurring from the administration of sulfanilamide has focused the attention of a number of investigators on the effects of the drug on the white blood cells. Although there exist several reports of mild to moderate leukopenia with neutropenia resulting from sulfanilamide (Bigler and associates, 1938; Britton and Hawkins, 1938; Smith, Weil and Bird, 1939), most workers are agreed that no significant changes occur in the white blood corpuscles due to a direct effect of the drug. For example, Long and Bliss (1939) noted no toxic effect of sulfanilamide on the leukocytes of 408 patients ill with various infections except for one individual in whom agranulocytosis developed. When the white blood cell count is elevated due to infection, it returns rapidly to normal as sulfanilamide brings the disease under control. If the infection is accompanied by a leukopenia, sulfanilamide does not further reduce the leukocyte count but rather allows its rapid return to normal (or even above) by arresting or curing the disease. Therefore Long and Bliss have concluded that ". . . with the exception of toxic changes associated with malignant neutropenia, there was no direct effect (*of sulfanilamide*) upon the white blood cells of patients . . . under treatment with this drug."

Severe neutropenia which may result in fatal agranulocytosis is one of the most serious toxic effects of sulfanilamide. Fortunately, this occurrence is rare. The complication is likely to occur after long continued medication with the drug, and in the 18 cases reviewed from the literature by Long and Bliss (1939), 12 appeared after sulfanilamide had been given for 17 days or longer. Likewise, of ten fatal cases of agranulocytosis assembled by Shecket and Price (1939), the length of time the drug was administered ranged from 15 to 30 days and large amounts were given. Often the white blood cell count does not begin to fall until several days after medication is stopped. Complete neutropenia unaccompanied by a significant degree of anemia occurs in the severe cases, and the clinical and hematological picture does not differ from that seen in idiopathic or aminopyrine-induced agranulocytic angina. Patients who upon recovery are retested for their sensitivity to sulfanilamide do not necessarily manifest recurrent toxic effects although Jones and Miller (1938) report an instance in which the patient responded with a distinct neutropenia on each of the two occasions when retesting was performed.

The mechanism of the agranulocytosis occurring after sulfanilamide is unknown, but is most likely dependent on the factor of personal idiosyncrasy. The reaction is rare and bears no relation to age, sex, dose or disease. The drug has been successfully given to patients with severe leukopenia due to a variety of infections, and to patients with aminopyrine-induced agranulocytosis. These facts should remove all doubt as to the safety of the drug regarding its effects on white blood cells provided the usual precautions are observed. These include careful and frequent examination of the total and differential leukocyte counts and use of the drug for the shortest period compatible with optimal therapeutic effects.

Treatment of severe neutropenia or agranulocytosis occurring from sulfanilamide includes immediate cessation of the drug, forcing of fluids, the use of nucleic acid derivatives and symptomatic measures (page 1147).

Hepatic Effects. During the course of, or subsequent to, sulfanilamide medication, an acute toxic hepatitis with jaundice and decreased liver function may develop (Long and Bliss, 1937; Hageman and Blake, 1937; Bannick and associates, 1938; Snodgrass and associates, 1938; Watson and Spink, 1940). Dermatitis, which may be exfoliative in character, occasionally accompanies the hepatitis (Garvin, 1938; Saphirstein, 1938). The hepatitis may take the form of an acute yellow atrophy (Cline, 1938). The damage to the liver cannot in all instances be attributed to sulfanilamide but there is indisputable clinical evidence that in certain patients the drug may cause hepatic injury. The cause is unknown and apparently bears no relation to dosage, type of infection or prior status of liver function. Indeed, the drug has been given to patients with cirrhosis or jaundice without untoward results (Cleveland, 1939). Although hepatitis due to sulfanilamide is rare, it is dangerous and has resulted in several fatalities. It must be distinguished from the jaundice which often occurs in the course of acute hemolytic anemia and which has an entirely different prognostic import, as well as from the jaundice occasionally present in patients severely ill with streptococcal and pneumococcal infections.

Treatment consists in cessation of sulfanilamide and forcing of fluids. As in patients with injury to the liver due to cinchophen, carbon tetrachloride or chloroform, other measures instituted include abundant carbohydrates, restriction of fats, intravenous or subcutaneous administration of solutions of glucose, and symptomatic therapy.

Miscellaneous Untoward Effects. The *kidney* apparently is not injured by sulfanilamide. For example, in rats with nephrotoxic nephritis, Smadel and Swift (1939) found that sulfanilamide given in therapeutic doses for long periods did not affect the course of the experimental disease. This result is in keeping with those of Hageman (1937), Rimington (1938) and Hawking (1937), all of whom have shown that the chronic administration of sulfanilamide to normal animals causes no histological changes in the kidneys. Patients with impaired renal function, however, excrete sulfanilamide slowly and this may result in retention of toxic concentrations of the drug. Rare complications occurring from the employment of sulfanilamide include *symptomatic thrombopenic purpura* and *aplastic anemia. Dyspnea* and *hyperpnea, tachycardia, abdominal and chest pains* and *hypopyrexia* have also been reported. The deaths occurring during the fall of 1937 from the use of a patented elixir of sulfanilamide were due to *diethylene glycol* employed as a solvent. The effect of sulfanilamide upon *spermatogenesis* in males ill with gonorrhea has received attention due to the report of Jaubert and Motz (1938) that the drug might injure sperm cells. Although others apparently have confirmed this finding, Heckel and Hori (1939) were unable to demonstrate any noteworthy effect of sulfanilamide on the total number or percentage of live spermatozoa when the drug was administered to 11 patients for two to eight weeks. Furthermore, Shettles (1940) found that human spermatozoa *in vitro* were unaffected with respect to activity or survival by concentrations of sulfanilamide or sulfapyridine well above those attained in body fluids during their therapeutic use.

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CHAPTER 58

SULFANILAMIDE AND RELATED SULFONAMIDE DRUGS

III. THERAPEUTIC USES OF SULFANILAMIDE

Sulfanilamide and related compounds, originally employed for the treatment of certain streptococcal infections, are now used in a wide variety of infectious diseases caused by bacteria and viruses. Chemotherapy with sulfonamide drugs is relatively new and thus revisions are constantly occurring in our knowledge and uses of these agents. For this reason, what is acceptable today may be obsolete tomorrow and the reader is cautioned to keep this fact in mind. Only the basic principles of sulfanilamide therapy can be presented here and the details must be sought in special texts and monographs. (*See* references at end of chapter.)

Before discussing the specific diseases in which sulfanilamide is of value, certain precautions and contraindications which allow for the safe and rational employment of the drug deserve attention.

Precautions and Contraindications. Sulfanilamide should be administered only to patients who are suffering from infections in which the drug can reasonably be expected to have a salutary effect. This often necessitates a bacteriological diagnosis, but at times one is justified in starting sulfanilamide therapy without waiting for the bacteriological report. This is especially true when the clinical diagnosis is clear and when delay may be detrimental to the patient's welfare. In numerous serious illnesses, early therapy with sulfanilamide is essential for success and the drug may therefore be started on the basis of the clinical diagnosis alone.

In order safely to administer sulfanilamide and to detect the earliest toxic manifestations, the drug should be given only under strict medical supervision and observation. The patient should be seen at least once daily. If this is impossible, as may well be the case in ambulatory patients with mild infections, the patient should be instructed concerning the detection of untoward effects and when to stop medication and notify his physician. Chills or fever, vomiting, jaundice, headache, deep or rapid breathing, weakness and sore throat constitute warning signals. Individuals who are hospitalized should have their temperature, pulse and respiratory rate recorded every four hours during the day. The hemoglobin and total white count should be determined at least every other day, and preferably each day during the first week because of the possible occurrence of acute hemolytic anemia particularly during this period. If the drug is continued beyond the tenth day, the leukocyte count should be followed daily because of the possible occurrence of agranulocytosis especially during the third and fourth weeks.

Therapy with sulfanilamide should be designed to meet the requirements of the individual case. Thus the doses and intervals of medication employed are varied with the severity of the infection. The blood level of sulfanilamide must be ascertained in order to insure optimal concentrations for the particular disease being treated and in order to avoid unnecessarily high levels. The patient's renal function must be known, and factors such as vomiting and abdominal distention which interfere with intestinal absorption should be closely observed. It is essential to administer sulfanilamide sufficiently long to establish a complete cure and prevent recurrence of the infection.

Contraindications to sulfanilamide are few. The main contraindication is the history of previous serious toxic reactions, such as agranulocytosis, acute hemolytic anemia, purpura hemorrhagica, drug fever, jaundice or severe dermatitis. If sulfanilamide is essential to save life, it may be given despite the aforementioned contraindications if the patient is hospitalized and observed very carefully. As stated above, sulfanilamide has been given without untoward effects to individuals with preexisting anemia, neutropenia and diseases of the liver.

Auxiliary Measures in Sulfanilamide Therapy. The evidence available appears to indicate that other drugs may safely be employed concurrently with sulfanilamide and that it is not necessary to proscribe such agents as barbiturates, magnesium sulfate, etc. Similarly, no special diet is indicated or contraindicated by the use of the drug. Fluids are restricted only if it is necessary to obtain a given urinary output in the treatment of patients with infections of the urinary tract. The forcing of fluids, other than when it is desired quickly to rid the body of sulfanilamide, may militate against obtaining a satisfactory blood level of the drug. A fluid intake of between 3000 and 4000 cc daily in the average febrile adult patient is probably adequate.

As emphasized by Long and Bliss (1939), the use of sulfanilamide has altered the indications for surgical intervention in a number of infections. Several instances illustrating this fact will be mentioned. Similarly, the significance of negative cultures obtained from purulent discharges of patients receiving sulfanilamide has undergone revision. A negative culture is of little value as an index for stopping treatment, and if the drug is prematurely withdrawn bacteria often rapidly reappear in the discharge.

Streptococcal Infections. Sulfanilamide is very effective in human infections due to the *beta hemolytic streptococcus.* It is particularly valuable against Lancefield's Group A hemolytic streptococci. Dramatic results are rarely seen when the invading organism belongs to Groups B, C or G. The status of sulfanilamide in the therapy of patients ill with *alpha hemolytic streptococci* (*Streptococcus Viridans*) cannot be stated. Although cases of uncomplicated septicemia due to *Streptococcus viridans* respond well to sulfanilamide, the results obtained in subacute bacterial endocarditis leave much to be desired and the enterococcus group does not appear to be susceptible to sulfanilamide. The drug also seems relatively ineffective in the therapy of infections caused by anaerobic streptococci and nonhemolytic streptococci.

Fortunately most serious streptococcal infections in man are due to Lancefield's Group A hemolytic streptococci. These organisms are highly susceptible to sulfanilamide and brilliant therapeutic results are often obtainable within two or three days of the beginning of drug administration. The therapy of a number of serious and fatal diseases caused by Group A organisms has been revolutionized by the advent of sulfanilamide, and some of the salient points in regard to the newer management of these diseases merit brief mention.

Infections of the Ears, Throat and Respiratory Passages. In the treatment of *acute otitis media* and *mastoiditis* of streptococcal origin, most observers are agreed that sulfanilamide is indicated and if used early and properly gives dramatic results. The duration of illness is considerably shortened and the incidence of mastoiditis is greatly decreased when the drug is employed in *acute otitis media*. For example, Hageman and Blake (1938) reported that in a series of 11 patients with otitis media due to the beta-hemolytic streptococcus, sulfanilamide therapy caused rapid subsidence of the disease and none developed mastoiditis or other infectious complications. These observations have been confirmed by Horan and French (1938, 1940) and others, and contrast with the high percentage of mastoidectomies required prior to the advent of sulfanilamide. For example, Horan and French (1940) reported that in a series of 621 cases of *acute suppurative otitis media* treated with sulfanilamide the incidence of mastoidectomies was only 3.4 per cent as compared with 22.7 per cent before the introduction of the drug. Doses designed to permit blood levels of four to eight mgm per cent (Table 54) are usually sufficient and are given until fever has been absent for two days. Somewhat smaller amounts are then continued until at least one week after all discharge has disappeared.

In *acute streptococcal mastoiditis*, Hageman and Blake (1938) noted in a series of 11 patients receiving sulfanilamide that nine cases subsided without surgical treatment, including one with marked meningeal reaction. Others have reported similar results. Intensive therapy is required when the decision is made to use sulfanilamide instead of resorting to surgery, and blood levels over 10 mgm per cent should be rapidly obtained (Table 53) and continued until all signs and symptoms have markedly improved, after which the dose may be halved. Small amounts should then be continued for a week or more after all evidence of the disease has disappeared. If surgical intervention is required, sulfanilamide should be continued in doses designed to yield blood levels of from four to eight mgm per cent and then small amounts given until convalescence is completed. In patients suffering from *chronic otitis media and mastoiditis*, Long and Bliss (1939) reported excellent results with sulfanilamide and point out that the drug should be administered even if bacteriological cultures from the purulent discharge fail to yield hemolytic streptococci. Doses of 0.5 gram four times daily (for adults) are usually adequate and should be continued for two to four weeks after the local process has completely healed.

In *acute hemolytic streptococcal sinusitis*, several workers have reported beneficial effects from sulfanilamide. Satisfactory results were obtained by Hageman and Blake (1938) in a series of nine cases with purulent sinusitis, only one (a patient with a mixed infection) requiring surgical intervention after sulfanilamide was started. The doses employed are adjusted to the severity of the infection.

In patients with *acute hemolytic streptococcal tonsillitis or pharyngitis*, sulfanilamide has yielded excellent results in the hands of a number of investigators. Doses designed to give a blood sulfanilamide level of from four to six mgm per cent are usually adequate but the dose should not be reduced until fever has been absent for a day or two, and small doses should be continued for the duration of convalescence. Long and Bliss (1939) treated a group of 46 patients with hemolytic streptococcal tonsillitis and pharyngitis and noted a rapid subsidence of symptoms and complete absence of complications due to the infection. The average duration of sulfanilamide therapy in their study was five days. Auxiliary measures consisted only of ice collars and warm throat irrigations. However, from the study of a small but controlled series of cases, Rhoads and Afremow (1940) could observe no beneficial effect of sulfanilamide on the severity or duration of the illness or on the incidence of complications, and they question the advisability of using the drug routinely in the average uncomplicated case of tonsillitis or pharyngitis due to hemolytic streptococci. More controlled studies of this type are required.

In cases of *tonsillar or peritonsillar abscesses* due to hemolytic streptococci, large doses of sulfanilamide are indicated as early as possible and blood levels over 10 mgm per cent should be quickly reached and maintained until the temperature has been normal for at least two days. The dose is then reduced and small amounts continued until convalescence is completed. Surgical drainage is indicated as soon as an abscess is clearly present, otherwise not.

In cases of *hemolytic streptococcal laryngitis and tracheitis*, sulfanilamide should be given early in large doses. Because of the severity and poor prognosis of the infection, one should not wait for a bacteriological diagnosis before starting the drug.

Erysipelas. Sulfanilamide therapy has proved satisfactory in erysipelas, and has changed entirely the management of this disease. Hageman and Blake (1938) noted in 27 patients that the duration of the disease was shortened considerably as compared with a control group (5.3 days vs. 13.9 days), that spread of the local lesion was less frequent (11 per cent vs. 66 per cent), and that infectious complications and mortality were reduced. Toomey (1938) noted a mortality of only four per cent in 74 patients treated with sulfanilamide as against 15.5 per cent in 1313 untreated controls and 13 per cent in 520 cases receiving erysipelas antitoxin. Similar beneficial results have been obtained by Snodgrass and his associates (1937, 1938) in Glasgow, Nelson and coworkers (1939) at Bellevue Hospital, Hoyne and collaborators (1939) at Cook County Hospital and Rantz and Keefer (1939) at the Boston City Hospital. Particularly striking is the reduction in mortality in infants and elderly people with erysipelas. Best results are obtained when sulfanilamide therapy is instituted on or before the third day of the illness.

In order rapidly to check the spread of lesions, bring the temperature down to normal, and relieve the toxic manifestations of the illness, doses of sulfanilamide which allow a blood level of from four to eight mgm per cent are usually sufficient. Larger doses may be required in infants and aged patients in whom bacteremia is more likely

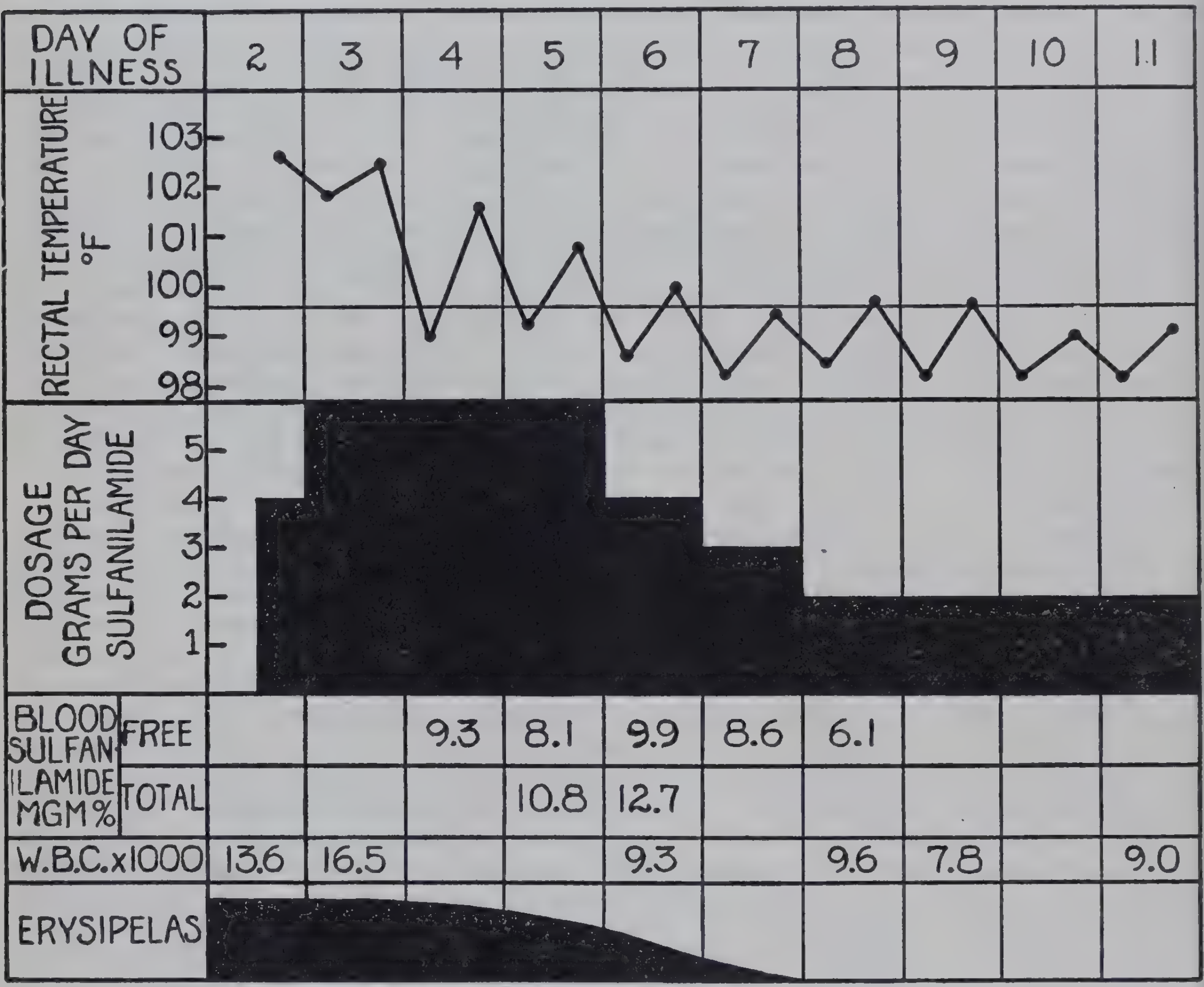

FIGURE 95. *The therapeutic effect of sulfanilamide in erysipelas.*

Male, aged 70, arteriosclerotic heart disease, admitted to the hospital on the second day of his acute illness. Two days before admission, a small red papule appeared on the left ear. Within 24 hours, the ear was swollen and the patient experienced a shaking chill. By the time of admission, the rash had spread to involve the left side of the forehead, face, neck and postauricular region. The patient was acutely ill and toxic, and presented a typical facial erysipelas. The blood examination showed a polymorphonuclear leukocytosis and the blood culture was negative. An initial dose of four grams of sulfanilamide was immediately given by mouth and then one gram administered every four hours thereafter day and night for three days. The spread of the lesion was immediately checked. Within 24 hours the patient felt and looked better, the rash had lost its fiery red appearance and then began to turn brown. Further progress in the regression of both the extent and intensity of the eruption is indicated in the solid black area at the bottom of the chart. The temperature defervesced satisfactorily (only the highest and lowest daily rectal temperatures are shown), and the patient was allowed out of bed on the tenth day. Observe that the level of free blood sulfanilamide was maintained between eight and 10 mgm per cent, and that the dose of drug was decreased gradually as improvement occurred. Small amounts were continued until convalescence was well under way. (Case data through courtesy of Dr. Joseph F. Sadusk, Jr., Yale University School of Medicine.)

to occur. After two days of normal temperature, the dose may be halved; but small amounts (1.2 grams daily for adults, 0.8 gram for children) should be continued until convalescence is complete in order to prevent recurrences. Definite abscess formation necessitates surgical drainage. Long and Bliss (1939) believe that the conventional local treatment with wet dressings should be discarded and advise that the skin lesions be kept slightly greased with a bland ointment. The clinical course of a typical case of erysipelas treated with sulfanilamide is charted in Figure 95.

Puerperal Sepsis. The original report by Colebrook and associates (1936, 1937) on the value of sulfanilamide in the treatment of puerperal fever has been amply corroborated by many investigators. Mortality figures vary greatly in this disease but the mortality is as high as 70 per cent for cases accompanied by bacteremia, peritonitis or extensive thrombophlebitis. Sulfanilamide therapy has greatly reduced this mortality, in some series to 20 per cent, and over one-half the patients with bacteremia may recover. The drug should be administered at the first sign of beginning infection without waiting for the report of bacteriological cultures, inasmuch as early therapy is essential and approximately 95 per cent of the cases are due to hemolytic streptococci, about 90 per cent of these being caused by Group A organisms (Colebrook and Purdie, 1937). The amount of sulfanilamide to be given depends on the severity of the infection. If bacteremia, peritonitis, parametrial extension or thrombophlebitis is present, the blood level should be kept between 10 and 15 mgm per cent and maintained there until fever has been absent for at least four days. The dose may then be reduced to one-half, this amount being continued for three or four days, and small doses should then be given until convalescence is quite complete. Patients with milder infections require less sulfanilamide and the reduction in dosage may be made more rapidly. If curettement is absolutely necessary before the infection has subsided, a blood level of sulfanilamide of at least 10 mgm per cent should be obtained before surgical intervention. Cervical smears may remain positive for streptococci long after clinical recovery has occurred. Puerperal infections due to anaerobic streptococci are resistant to sulfanilamide therapy.

Streptococcal Meningitis. In meningitis due to hemolytic streptococci, truly brilliant results have been obtained with sulfanilamide therapy. The first reports of success were those of Schwentker and associates (1937) and Arnold (1937), and these were soon followed by many others. The mortality in this disease prior to the introduction of sulfanilamide was between 97 and 100 per cent, but has been reduced to approximately 35 per cent (Long and Bliss, 1939). Toomey and Kimball (1939) report 10 recoveries in 12 cases treated with sulfanilamide as compared with one recovery in 11 patients prior to sulfanilamide. Of 60 sulfanilamide-treated cases reported in the literature and cited by Keefer (1938), 47 recovered (mortality of 22 per cent), and Sappington and Favorite (1939), from their own experience and a review of the literature, report a similar reduction in mortality. These results approach the miraculous.

Large doses of the drug designed to raise the blood level quickly to 15 mgm per cent are imperative as soon as the diagnosis is made, and the spinal fluid level of sulfanilamide will then be about 10 to 12 mgm per cent. These concentrations should be maintained until spinal fluid cultures have been negative for three consecutive days and the temperature has been normal for a similar period. The daily dose of drug may then be gradually decreased but small doses should be continued until convalescence is complete in order to avoid the recurrences which are likely to occur. The character of the spinal fluid and its cell count also serve as a guide to dosage when frequent bacteriological studies are not feasible. Lumbar puncture should be done at least once daily and the appropriate studies performed on the fluid obtained. No evidence, either favorable or unfavorable, exists for the use of a one per cent solution of sulfanilamide administered intrathecally. If an otogenic or paranasal sinus focus exists, which requires drainage, and when surgical intervention will not prove a hazard to the patient, the focus may be drained after sulfanilamide has been started. Relapses require that sulfanilamide again be administered in full doses.

Streptococcal Peritonitis. Peritonitis due to the streptococcus is nearly always fatal, but recoveries have been reported as a result of the use of sulfanilamide. Long and Bliss (1939), on the basis of their experience in several cases of "primary" hemolytic streptococcal peritonitis, advise that whenever feasible the diagnosis should be made by abdominal paracentesis rather than surgical incision and that intensive therapy with large doses of sulfanilamide be given in order to obtain a blood level of 15 mgm per cent. Parenteral administration is usually necessary and full doses should be maintained until recovery is well under way. The amount may then be reduced and small doses continued until convalescence is complete. Surgical procedures should be avoided if possible.

Streptococcal Pneumonia. Sulfanilamide has proved of great benefit in the therapy of pneumonia due to hemolytic streptococci. Hageman and Blake (1938) reported that all in a group of seven patients recovered and only one required thoracotomy, despite the fact that before sulfanilamide was started three had positive blood cultures and two of these already had purulent complications. Long and Bliss (1939) record their results in eight cases of streptococcal pneumonia. All recovered, although two patients who had a purulent pleurisy upon admission to the hospital required surgical drainage of empyemas. Intensive sulfanilamide therapy designed to give blood levels of from 10 to 15 mgm per cent is recommended and the large doses should be continued until fever has been absent for three days and pneumonic resolution well under way. The dose may then be reduced gradually but small amounts should be administered until convalescence is completed.

Empyema. Sulfanilamide has proved of distinct value in the treatment of pleurisy due to the hemolytic streptococcus, and surgical intervention in streptococcal empyemas may often be entirely circumvented by the use of the drug. Large doses should be prescribed early (Table 53) so that levels of sulfanilamide of from eight to 10 mgm per cent will be present in the pleural exudate. Intrapleural injection of solution of sulfanilamide has not been proved of value. Intensive treatment is continued until fever is absent for three days and the infected pleural exudate has disappeared. Medication may then be decreased but small doses should be given until convalescence is complete. Thoracotomy to establish drainage may be required if the empyema has not cleared within ten days despite proper sulfanilamide therapy, and the drug is then continued until recovery is complete. Sulfanilamide combined with frequent thoracenteses, however, often prevents the necessity of immediate thoracotomy and may make surgical intervention entirely unnecessary.

Streptococcal Septicemia. In patients with hemolytic streptococcal septicemia secondary to infection elsewhere or without discoverable focus, intensive sulfanilamide therapy should be quickly instituted and continued until fever is absent and blood cultures negative for three consecutive days. The dose may then be reduced gradually and small amounts administered until recovery is complete.

Streptococcal Osteomyelitis. Sulfanilamide has definite value in the treatment of both acute and chronic hemolytic streptococcal osteomyelitis and has markedly decreased the incidence of protracted chronic phases of the disease. Both Lockwood and coworkers (1938) and Long and Bliss (1939) reported complete cures by the use of sulfanilamide in refractory cases which had progressed for five to six years. Long and Bliss agree with Key (1938) that sulfanilamide may be given to children under two years of age without waiting for blood or aspiration cultures to prove a streptococcal etiology, but that positive cultures should first be obtained in older individuals. Intensive drug therapy is administered for acute cases and moderate doses for chronic cases. The absence of streptococci in the discharge of patients receiving sulfanilamide does not signify complete disappearance of the organism and the drug should be continued until all sinus tracts have completely closed. Sulfanilamide renders unnecessary the excision of sinus tracts in chronic cases, but the indications for surgical intervention in acute cases since the advent of sulfanilamide therapy are undetermined. Operative procedures are often entirely avoided by the early and proper use of the drug.

Scarlet Fever. The value of sulfanilamide in the therapy of scarlet fever is not established. Hageman and Blake (1938) noted that the toxic phase of the disease in a small series of patients seemed unaffected by sulfanilamide but that septic complications did not occur. Schwentker and Waghelstein (1938) did not observe that the drug altered the course of the disease. Wesselhoeft and Smith (1938) noted no decrease in the incidence of complications in 360 sulfanilamide-treated cases as compared with 461 untreated controls and failed to demonstrate any reduction in the toxicity as indicated by the duration of fever or intensity of the eruption.

Several observers, however, have reported quite favorable results. Sako and coworkers (1938) record a marked diminution in complications among 100 cases of scarlet fever treated with sulfanilamide as compared with 100 control cases (four vs. 41 instances), but they did not observe acceleration of the rate of recovery from the acute toxic phase of the disease. Bozalis and Barnett (1940) recorded favorable results and no deaths in 300 consecutive cases of scarlet fever treated with sulfanilamide and, in severely toxic patients, with sulfanilamide and scarlet fever antitoxin.

Long and Bliss (1939), in comparing the effects of sulfanilamide and antiserum, state that, "The modes of action of the two agents are entirely different; sulfanilamide prevents the growth and spread of the bacteria, while serum neutralizes the toxic products of their growth which manifest themselves in the toxemia, fever, and rash of the disease. One would, therefore, not expect to see, following the use of sulfanilamide, the rapid abatement of the signs that are affected by antiserum. At the same time, by restricting the growth of the streptococci, sulfanilamide limits the amount of toxic substances liberated so that the ultimate effect, again, is the subsidence of the toxemia. Serum, on the other hand, has little effect on the local infectious process." Long and Bliss emphasize that the earlier sulfanilamide is started in the course of the disease, the more striking will be the results obtained. They report on the use of the drug in medical students and nurses who were treated at the inception of the rash or, in certain instances, even before the appearance of the rash. Sulfanilamide apparently shortened the duration of fever, rash and general toxic symptoms, and in many cases practically aborted them so that only careful observations of transient punctate erythemas and the fact that positive Dick tests became negative within two or three weeks allowed any certainty that scarlet fever was actually being treated.

Doses designed to yield blood levels of from four to eight mgm per cent are usually sufficient and are continued until fever has been absent for two days. Medication is then reduced over a period of a week and small doses continued until convalescence is completed. Some investigators advise that sulfanilamide therapy be supplemented with antitoxin in patients severely ill with scarlet fever. Sulfanilamide in doses of 0.5 gram three times daily has also been recommended as a *prophylactic measure* in persons exposed to the disease.

Rheumatic Fever. Sulfanilamide has been employed in rheumatic fever despite the lack of indisputable evidence that the disease is caused by hemolytic streptococci. In eight cases of rheumatic fever in which they administered sulfanilamide, Swift and coworkers (1938) not only observed no benefit from the drug but also observed that toxic effects seemed to be intensified, and Massell and Jones (1938), from their experience with a series of 58 cases, decided that sulfanilamide was without value in the acute stage of the disease. Long and Bliss (1939) agree with this opinion.

Due to the frequent occurrence of hemolytic streptococcal infections in patients with rheumatic fever, Coburn and Moore (1939) studied the *prophylactic value* of sulfanilamide. They found that the drug did not prevent rheumatic recrudescences when given to rheumatic subjects after the onset of streptococcal throat infections, but that it seemed of value when given prophylactically to 80 rheumatic children, 79 developing no hemolytic streptococcal infection or signs of rheumatic activity during the period of administration. In a control group of 400 untreated rheumatic subjects, 35 per cent developed group A hemolytic streptococcal throat infections. From their limited series, Thomas and France (1939) also report that the continuous prophylactic use of sulfanilamide during the winter months in patients with rheumatic heart disease may be of benefit in preventing rheumatic recrudescences by controlling antecedent acute beta hemolytic streptococcal infections. Sulfanilamide may also be given prophylactically to patients with rheumatic heart disease prior to dental extractions or tonsillectomies (Long and Bliss, 1939), the object being to prevent the possible occurrence of a subacute bacterial endocarditis.

Subacute Bacterial Endocarditis. Sulfanilamide has been tried in relatively few cases of infection due to the alpha hemolytic streptococcus (*Streptococcus viridans*). Although sporadic "cures" have been reported in patients with subacute bacterial endocarditis as a result of sulfanilamide therapy, the results are not convincing. Spink and Crago (1939) noted that sulfanilamide may produce temporary sterilization of the blood in patients with bacteriemia but in only one of 11 cases of *Streptococcus viridans* subacute bacterial endocarditis did they observe definite improvement. Barnett and coworkers (1939) used very large doses of sulfanilamide in three cases without benefit. Krusen, Bennett and Herrell (1940) noted definite beneficial effects from sulfanilamide therapy combined with fever therapy in six patients with subacute bacterial endocarditis, but death eventually occurred in all. Steele (1940) reported that sulfanilamide therapy had no effect on the general course of 13 cases of the disease.

Long and Bliss (1939) have treated 60 patients with subacute bacterial endocarditis and state that five were apparently "cured" and were enjoying relatively normal lives after prolonged therapy with sulfanilamide. The five were typical cases and showed several positive blood cultures for alpha hemolytic streptococci. Long and Bliss comment on the frequency with which they observed a decrease in fever, pulse rate and number of organisms in the blood as a consequence of sulfanilamide therapy. They suggest that all patients should continuously receive large doses of the drug (blood levels of from 10 to 15 mgm per cent) until a "cure" or death occurs, provided treatment is tolerated and despite the protracted persistence of positive blood cultures. If and when the blood becomes sterile, sulfanilamide should not be discontinued until three months have elapsed. Because sulfanilamide retards bacterial growth, all cultures should be followed for at least three weeks. The results obtained with a combination of heparin and sulfonamide drugs appear sufficiently promising to warrant further trial in patients with bacterial endocarditis (pages 1084, 1145).

Other Streptococcal Infections. Other infections due to the hemolytic streptococcus such as *adenitis, Ludwig's angina, cellulitis, chronic skin ulcers* and *chronic pyodermia* have yielded satisfactorily to sulfanilamide therapy. Lymphadenitis due to hemolytic streptococci regresses when moderate doses of sulfanilamide are administered and need no longer be treated with compresses and incision. Recovery has been reported in three of the five patients of Long and Bliss (1939) treated with sulfanilamide for streptococcal Ludwig's angina. They believe that the prognosis is so grave that the drug should be given intensively and early even though a bacteriological culture is lacking. Surgical incision should be performed only when an accumulation of pus is definitely present and localized.

Meningococcal Infections. Sulfanilamide has proved valuable in the treatment of meningococcal infections including those of the *meninges, joints, conjunctivae* and *blood stream.*

Meningitis. In meningococcal meningitis, numerous investigators have reported that sulfanilamide gives results at least as satisfactory as those obtainable with antiserum. In series of cases sufficiently large to be statistically significant, Waghelstein (1938), Muraz and associates (1938) and Banks (1939) found that sulfanilamide reduces mortality, complications and incidence of recurrent infections. Waghelstein reported a mortality of 15 per cent in 72 patients treated with sulfanilamide and 27 per cent in 368 control patients receiving serum alone. He noted a reduction in recurrences after sulfanilamide therapy and a marked decrease in the number of fatalities occurring within the first day of treatment. Banks noted a mortality of 12 per cent and 13 complicated cases in a series of 65 patients treated intensively with serum and given varying (inadequate) amounts of sulfanilamide, whereas in a series of 31 patients treated with sulfanilamide alone no death and few complications occurred. Muraz and associates, working under unfavorable conditions among natives of French Nigeria, obtained excellent results with sulfanilamide during an epidemic of meningococcal meningitis. For example, the number of fatalities among 49 persons receiving intrathecal serum was 22 per cent, whereas among 271 receiving only sulfanilamide by mouth it was 11 per cent.

It thus appears that sulfanilamide alone provides a most satisfactory method of treating the disease although in some patients the combined use of drug and antiserum may be indicated. Medication should be intensive, large doses being given in order rapidly to obtain blood levels of 15 mgm per cent and spinal fluid levels of from 10 to 12 mgm per cent. Large doses are continued until the temperature is normal and spinal fluid cultures negative for three consecutive days, and may then be decreased gradually during convalescence but the drug should not be discontinued until the patient is ambulatory. Only in this manner is it possible to prevent recurrences, which, when they appear, must again be treated as intensively as was the original infection. Intrathecal administration of the drug has not been proved of definite value. Lumbar punctures need not be performed repeatedly but only when evidence of increased intracranial pressure necessitates the procedure. If not too strenuous for the patient, spinal fluid may be withdrawn once daily for microscopic study and culture. The spinal fluid is usually cleared of organisms in 24 to 48 hours. The clinical course of a typical case of meningococcal meningitis treated with sulfanilamide is shown in Figure 96.

Meningococcemia. This disease is likewise quickly abolished by sulfanilamide, whether or not associated with meningitis. Long and Bliss (1939) observed five patients with acute meningococcemia without meningeal signs in whom large amounts of sulfanilamide resulted in prompt cures.

Gonococcal Infections. Soon after the discovery of the clinical efficacy of sulfanilamide in meningococcal infections the drug was successfully tried in gonococcal diseases (Dees and Colston, 1937; Reuter, 1937; Herrold, 1937), and numerous reports testify to its efficacy. Infections caused by the gonococcus and yielding to sulfanilamide therapy include *urethritis, prostatitis, epididymitis, salpingitis,* *cervicitis, vulvovaginitis* (in young girls), *ophthalmitis, arthritis, endocarditis, meningitis and peritonitis.*

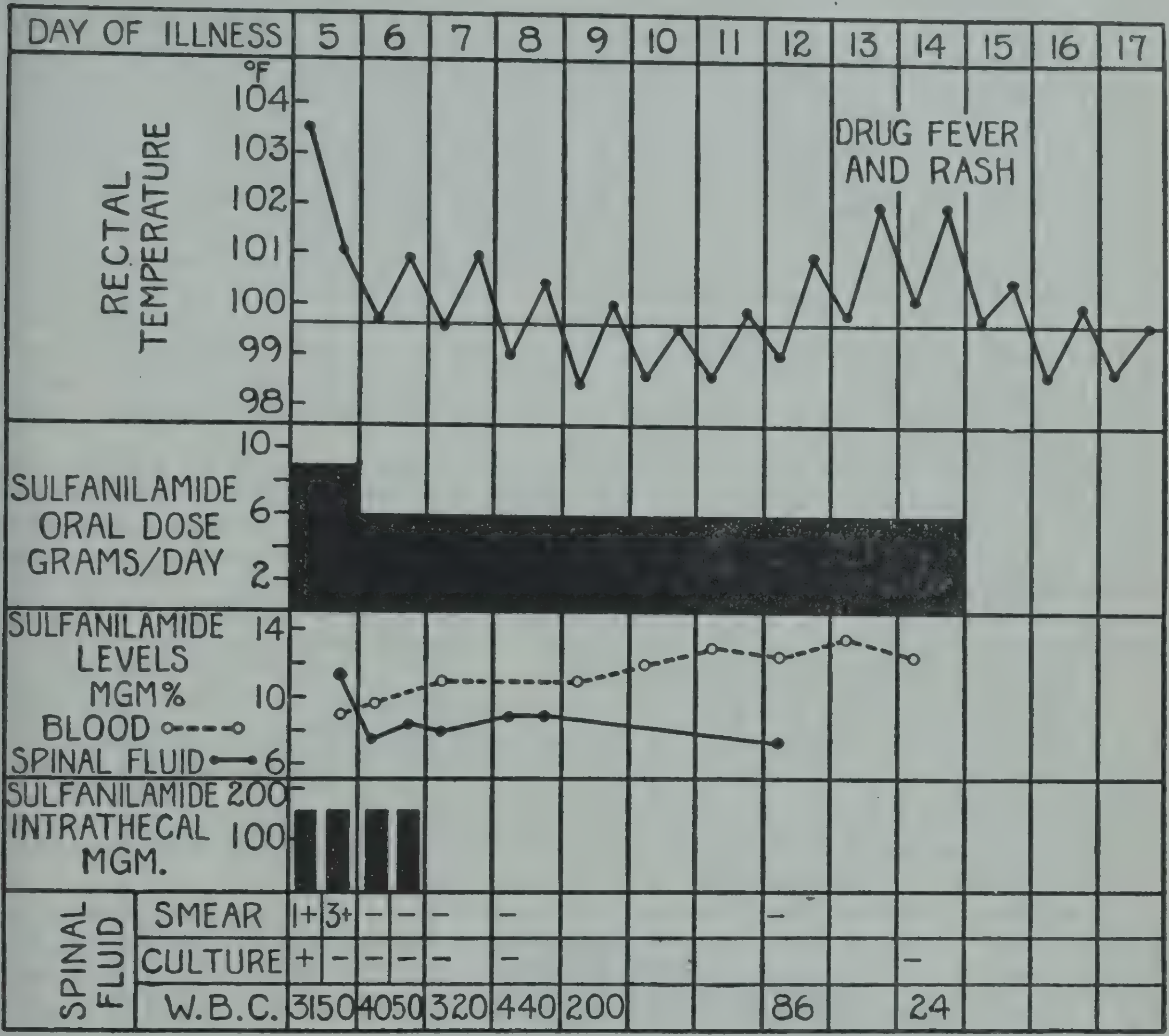

FIGURE 96. *The therapeutic effect of sulfanilamide in meningococcal meningitis.*

Male, aged 19, entered the hospital on the fifth day of his illness. Patient developed sore throat, cough and headache four days prior to admission. The following day, malaise, chills, severe headache, stiff neck, blurred vision and diplopia were noted. Symptoms progressed until the headache became intolerable. Examination on admission revealed typical signs and symptoms of acute meningitis. The spinal fluid showed the meningococcus on smear and culture and 3150 white cells per c. mm., predominantly polymorphonuclear. The blood culture remained sterile. A diagnosis of meningococcal meningitis was made and intensive sulfanilamide therapy immediately started. Four grams were given orally as an initial dose and one gram was administered each four hours thereafter day and night. In addition, intrathecal injections of approximately 20 cc each of an 0.8 per cent solution of the drug were given, two on the first day and two on the second day. The blood level of free sulfanilamide was maintained between 10 and 14 mgm per cent; that of the spinal fluid, between eight and nine mgm per cent, the initial high level being due to the intrathecal injections. The patient was greatly improved within 24 hours after admission; the temperature fell precipitously (only the highest and lowest daily rectal temperatures being shown), and symptoms and signs of the disease diminished. The rapid sterilization of the spinal fluid and decrease in its cell count are shown in the chart. Recovery was uneventful until the tenth day, when drug fever developed (*compare* with Figure 93). This was mistaken for a recrudescence of the disease until an erythematous rash appeared and a lumbar puncture was performed, the spinal fluid showing only a few lymphocytes and no organisms. Sulfanilamide medication was stopped and the fever and rash quickly disappeared. (Case data through courtesy of Dr. Joseph F. Sadusk, Jr., Yale University School of Medicine.)

Gonorrhea. Due to the high incidence of this infection, considerable interest centers about its treatment with sulfanilamide and the economic and public health aspects of the disease as affected by the newer therapy. So numerous are the many clinical papers on the use of sulfanilamide in gonorrhea in the male and female and so divergent are the results obtained by various observers that years may be required accurately to state the true value of and indications for the drug. Although the early sanguine reports have not been entirely substantiated, nevertheless the use of sulfanilamide has opened a new era in the treatment of gonorrhea.

For reasons not adequately understood, sulfanilamide is apparently more effective when its administration is withheld until one week or more has elapsed after the onset of the acute infection (Vest and coworkers, 1938; Mahoney and collaborators, 1938; Cokkinis and McElligott, 1938; Dees, 1938; Ferguson and associates, 1939; Van Slyke and Mahoney, 1940). It has been suggested that the body then has had sufficient time to acquire some immunity to the gonococcus. However, Pelouze (1939), on the basis of a well controlled study of a small series of cases, could demonstrate no clinical differences between a group of 54 males given sulfanilamide within 48 hours of the onset of the disease and a group of 51 cases in which sulfanilamide therapy was deferred for seven to 14 days. He therefore believes that it is preferable to start sulfanilamide early in patients with acute gonococcal urethritis.

Sulfanilamide therapy appears to increase the bactericidal power of the patient's blood for the gonococcus (Spink and Gaston, 1938) but independently of the development of specific bacteriolytic antibodies (Keefer and Rantz, 1938). Indeed, Keefer and Spink (1937) offer evidence to indicate that the drug *per se* is bactericidal *in vivo* under certain conditions. Furthermore, there is no correlation between the blood and urine concentrations of the drug and either clinical responses or changes in the local infectious process in the urethra (Vest and coworkers, 1938). Obviously many features of the action of the drug in gonorrhea require further study.

Although many different dosage plans have been proposed, it would appear that therapy in ambulatory male patients for approximately four weeks is adequate, and that from four to five grams daily (in four equally divided doses) should be given for the first week or ten days. This may then be decreased to three grams daily for a week and followed by 1.2 grams daily for two weeks. The dose should be increased if symptoms recur. (*See* Dees and Colston, 1937; Colston, Dees and Harrill, 1937; Orr, 1937; Alyea and associates, 1938; Cokkinis and McElligott, 1938; Pelouze, 1940.)

Gonorrhea in females often responds more readily to sulfanilamide therapy than in males and the dosage for ambulatory women is four to five grams daily (in four equally divided doses) for the first week and three grams daily for the following ten days or two weeks. Long and Bliss (1939) are inclined to believe that in both males and females the maintenance of blood levels of sulfanilamide of from five to seven mgm per cent during the period of treatment should be sufficient.

The results obtained with sulfanilamide include rapid apparent cure of the gonorrhea, rapid subsidence of the acute complications of a recent gonorrheal infection, and decrease in the incidence of extensions of the infection to the posterior urethra and prostate. Dees and Young (1939), in a review of 2727 sulfanilamide-treated cases of gonorrhea in males collected from the literature, report that 68 per cent are classified as immediate cures and four per cent as "delayed cures." Among 1123 cases, reinfection or recurrence is recorded in only 2.5 per cent, and in 1308 cases, definite progression or extension of the disease to the adnexa while undergoing therapy is recorded in only three per cent. Thomas (1939), from a review of the literature, collected 4762 cases of gonococcal infection treated with sulfanilamide. These cases are independent of those included in the aforementioned analysis of Dees and Young. Cures are recorded in 74 per cent.

In the male, sulfanilamide is probably as effective alone as when combined with local measures such as instillations, irrigation, etc. Although good results have been reported with combined sulfanilamide and fever therapy, it appears that fever treatment should be reserved for patients refractory to sulfanilamide.

In women, sulfanilamide is even more successful in the therapy of acute gonorrhea than in men, and symptoms of the infection disappear rapidly, the average course of treatment being less than two weeks in duration. The incidence of complications is greatly reduced and complications already present are readily cured. Gonococcal salpingitis and peritonitis are readily controlled (Grodberg and Carey, 1938; Randall, Krusen and Bannick, 1938). Long and Bliss (1939) observed seven women with *gonococcal peritonitis* who improved when large doses of sulfanilamide were administered.

A number of investigators have warned that the use of sulfanilamide in the treatment of gonorrhea carries with it the danger of producing asymptomatic carriers who may spread the infection. Men may infect women who in turn remain asymptomatic carriers with no idea that they are infected until they transmit the disease to others. This is due to the fact that sulfanilamide changes the characteristics of the gonorrheal slide, and the reliable criteria of cure employed before the advent of sulfanilamide therapy are no longer applicable. Pelouze (1938, 1940) and Dees and Young (1939) in particular warned against the social and public health hazard of this situation and outlined the technic for determin-

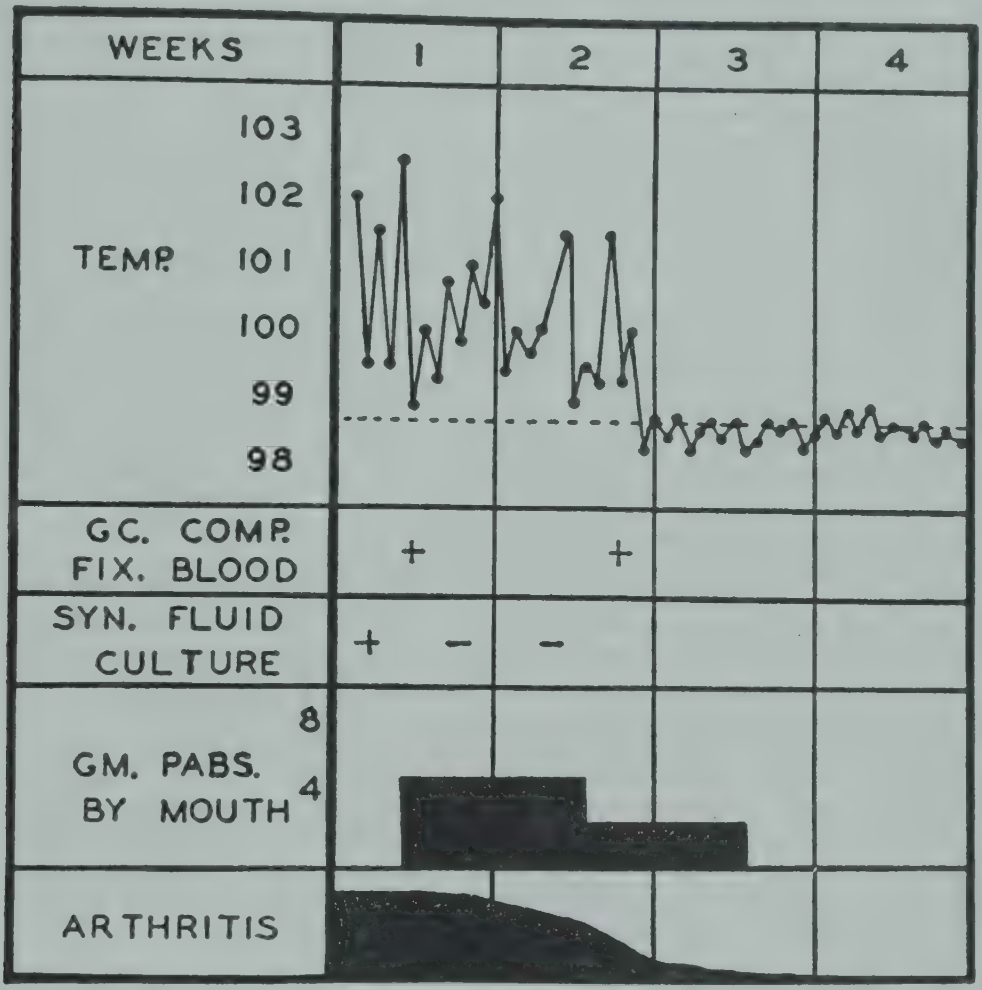

FIGURE 97. *The clinical efficacy of sulfanilamide in the therapy of acute gonococcal arthritis.*

Male, aged 40 years, well until two weeks prior to admission to the hospital when he developed an acute upper respiratory infection which subsided within four days. Five days before admission, his right knee became stiff and painful and the next day it was greatly swollen. The patient had gonorrhea 20 years previously. Examination revealed acute arthritis of the knee, high fever, and a leukocytosis of 12,500 per c. mm. No gonococci were recovered from the urethra or prostatic fluid, but synovial fluid obtained on the first tapping revealed infection with gonococci and the gonococcal complement-fixation test on the blood was positive. Following the institution of sulfanilamide therapy (PABS = para amino benzene sulfonamide), the blood and synovial fluid levels of the drug rose so that at the time of the next tapping the joint fluid was sterile and contained 5.7 mgm% of the drug. Two days later, the synovial fluid contained 7.7 mgm% of sulfanilamide. The fever gradually subsided as illustrated in the chart, and the arthritis disappeared so that the patient was well and without disability at the end of four weeks. Sulfanilamide can sterilize the synovial fluid before the temperature returns to normal, and the arthritis begins to improve after the disappearance of the organisms. The case also illustrates the long latent period which may exist between the primary infection and the arthritis, the inability always to find organisms in the urogenital tract and the not infrequent occurrence of gonococcal arthritis following an attack of acute sore throat. (After Keefer and Rantz, 1939. Courtesy of the *American Journal of the Medical Sciences.*)

ing whether patients who have received sulfanilamide are cured of their infection. Silver and Elliott (1939), from their experience with sulfanilamide therapy in 1625 cases of gonorrhea, point out that the slight risk of death from the drug is outweighed by the disabling effects, economic loss and sterility due to gonorrhea, and the ultimate mortality in women (one to two per cent) who undergo the pelvic operations the disease may necessitate.

Gonococcal Vulvovaginitis. Sulfanilamide in the hands of certain clinicians has given good results in the treatment of young girls suffering from gonococcal vulvovaginitis (Brown, 1938; Hoffman and coworkers, 1938; Cohn and associates, 1940; and others). Thus, Adler (1938) recorded success in 16 of 22 cases, the duration of the disease and the necessity for local therapy both being decreased. Others have not been able to verify these good results (Grodberg and Carey, 1938; Long and Bliss, 1939). Obviously the ultimate value of the drug in this distressing infection in children cannot yet be stated.

Gonorrheal Ophthalmia. Good results have been reported by many investigators using oral sulfanilamide therapy in both children and adults with gonococcal conjunctivitis (Newman, 1937; Willis, 1938; Fernandez and Fernandez, 1938; Michels, 1938; Adler, 1938; Barbour and Towsley, 1939; and others). Doses designed to give blood levels of from five to eight mgm per cent are adequate. Local measures should perhaps be combined with sulfanilamide therapy.

Gonococcal Arthritis. Dramatic responses have been obtained with sulfanilamide therapy in patients with acute and subacute gonococcal arthritis. Within two to three days, the infected joint fluid is sterilized and evidence of the disease rapidly subsides, joint function being completely restored. For example, Keefer and Rantz (1939) report 12 recoveries and two instances of improvement in a series of 14 cases treated with the drug. This confirms the experience of others (Colston and coworkers, 1937; Keefer and Spink, 1937; Coggeshall and Bauer, 1938; and others). Doses designed to give blood levels between five and 10 mgm per cent should be administered and proper local measures employed. Hyperpyrexia may perhaps be used in those cases not responding satisfactorily within seven to 10 days. Recurrences of fever, arthritis and urethritis may follow withdrawal of the drug. Keefer and Rantz advise that sulfanilamide be administered until the sedimentation rate of the blood is normal and, if the complement-fixation test is negative, until it is positive. The clinical course of a patient with acute gonococcal arthritis is shown in Figure 97. Chronic cases respond poorly to sulfanilamide.

Gonococcal Endocarditis. Intensive and continued sulfanilamide therapy is indicated in patients with gonococcal endocarditis. Futcher and Scott (1939), however, reported three fatalities in four patients treated with sulfanilamide for gonococcal endocarditis.

Gonococcal Meningitis. Intensive therapy with sulfanilamide is indicated in the rare event of gonococcal meningitis (Marvin and Wilkinson, 1938; Branham and associates, 1938). Sappington and Favorite (1939) record six recoveries in a series of eight patients treated with the drug for meningitis due to *Neisseria intracellularis.*

Urinary Tract Infection. The value of sulfanilamide in the therapy of urinary tract infections is firmly established and the drug has definitely relegated mandelic acid to a second place in the list of urinary anitseptics of choice. The original work of Helmholtz and Osterberg (1937, 1938) in this field has been amply confirmed in its essential features by all subsequent investigators (Buchtel and Cook, 1937; Long and Bliss, 1938; Chute, 1938; Herrold, 1938; Vest and associates, 1938, 1939; Braasch, 1939; Crenshaw and Cook, 1939; and others).

Sulfanilamide varies in its efficacy against different microorganisms causing infection of the urogenital tract. Therefore, before starting therapy one should establish the nature of the infection by a Gram stain of smears of the centrifuged urinary sediment and by a culture of the urine. The drug is effective against *E. coli, Aerobacter aerogenes, Salmonella, Shigella, B. influenza, Staphylococcus albus* and *aureus, Pseudomonas aeruginosa* and *Proteus vulgaris.* It is ineffective against *Group D hemolytic streptococci, Streptococcus fecalis* and non-hemolytic, green and hemolytic *enterococci.*

The action of sulfanilamide in urinary tract infections is both bacteriostatic and bactericidal. As explained previously, the high concentrations of sulfanilamide obtained in the urine combine with the unfavorable environment offered by the urine to eradicate the infection. One can predict the concentration of free and conjugated sulfanilamide to be found in the urine when the daily dose of drug and intake of fluids are known. For example, since approximately 90 per cent of the drug is excreted in the urine, 4.5 grams will be excreted daily with a dose level of 5.0 grams daily given to an adult. If the fluid intake is adjusted to allow a 24 hour urinary output of 1000 cc (fluid intake of about 1500 cc daily), the concentration of sulfanilamide in the urine when balance is established (*i.e.*, after three to four days) will be 450 mgm per cent. Inasmuch as half the excreted drug is in the free form, the concentration of free sulfanilamide will be approximately 225 mgm per cent (Figure 90). This basic information may be used in the calculation of any desired urinary concentration of sulfanilamide by controlling the daily ingestion of drug and fluids. The assumption, of course, is that renal function is adequate. The treatment of most urinary infections requires concentrations of sulfanilamide in the urine of from 200 to 250 mgm per cent for seven days in order to obtain optimal results, but patients differ considerably in this respect. The daily dose of drug is administered in four equally divided portions.

While sulfanilamide exerts its antibacterial action in the urine at all pH's encountered clinically, there is considerable clinical and experimental evidence to indicate that better results may be obtained when the urine is slightly alkaline. Although some investigators (Kenny and associates, 1937; Herrold, 1937; Long and Bliss, 1938; Rantz and Keefer, 1940) failed to demonstrate any change in bactericidal activity of sulfanilamide by altering the reaction of the urine, others (Helmholtz and Osterberg, 1937; Sickler and Cook, 1939) observed a potentiating action of alkaline urine. For example, Sickler and Cook found that urine collected from normal persons taking sulfanilamide and adjusted to various pH's manifested greater bactericidal effect *in vitro* against a variety of organisms including 13 strains of *E. coli* at pH 7.7 than at 6.2 or 7.0. It may therefore be wise in certain cases to administer sodium bicarbonate (two to five grams daily) with sulfanilamide in order to obtain a slightly alkaline urine. Alkaline urine in itself, as it is formed in the body, is not bactericidal or bacteriostatic.

The results of sulfanilamide therapy are most satisfactory. More than 90 per cent of uncomplicated bacillurias can be entirely cured, and the urine becomes sterile in from two to seven days. Often patients are cured whose infections resisted other therapy for many years. Mixed infections and coccal infections, as a rule, respond less readily. Cure can be established only by urine cultures and medication is best continued until two catheterized specimens of urine taken at four day intervals are negative. Changes in the cytology of the urinary sediment do not provide an adequate guide to the response of the infection to therapy, and whenever possible urine cultures should be performed. Results are distinctly inferior when renal function is poor, and large doses should then be avoided and the blood concentration followed. Patients with lithiasis, chronic pyelonephritis or obstruction rarely obtain a permanent cure. Urinary infection associated with chronic prostatitis responds well to sulfanilamide, and the drug has been found of value to use prior to prostatic resection. Indeed, it has been successfully employed both before and after a variety of surgical procedures upon the urogenital tract. It has also been used in pyelitis of pregnancy.

Sulfanilamide differs in several important respects from mandelic acid (page 839). Sulfanilamide has the advantage that it is effective at all urinary pH's whereas mandelic acid is effective only in distinctly acid urines. Sulfanilamide is cheap and well tolerated by most patients whereas gastro-intestinal upsets are frequent during mandelic acid therapy. Sulfanilamide can be administered by several routes whereas the acid can be taken only orally. Sulfanilamide can be employed without danger of provoking marked acid-base balance disturbances, a distinct advantage in acutely ill and febrile patients, especially children, and in patients with impaired renal function. Finally, sulfanilamide cures urinary infections caused by certain bacteria which are unaffected by mandelic acid, notably urea-splitting organisms such as *B. proteus*. On the other hand, the acid is quite effective against hemolytic or non-hemolytic *enterococci*, whereas sulfanilamide does not inhibit these organisms.

Gas Bacillus Infection. Sulfanilamide has revolutionized the therapy of infections caused by *Cl. welchii* with a consequent saving of life and limb. Bohlman (1937) and Kennedy (1938) both reported on the efficacy of sulfanilamide in controlling gas gangrene, marked improvement being noted promptly after administration of proper doses of the drug. Long and Bliss (1939) had similarly successful results and believe that the indications for surgery are now quite different than before sulfanilamide was available. The responsibility rests on the surgeon who advises amputation of an infected extremity rather than therapy with sulfanilamide, and removal of a limb should now be reserved for far advanced cases or when injury is so severe as to make restoration of function impossible.

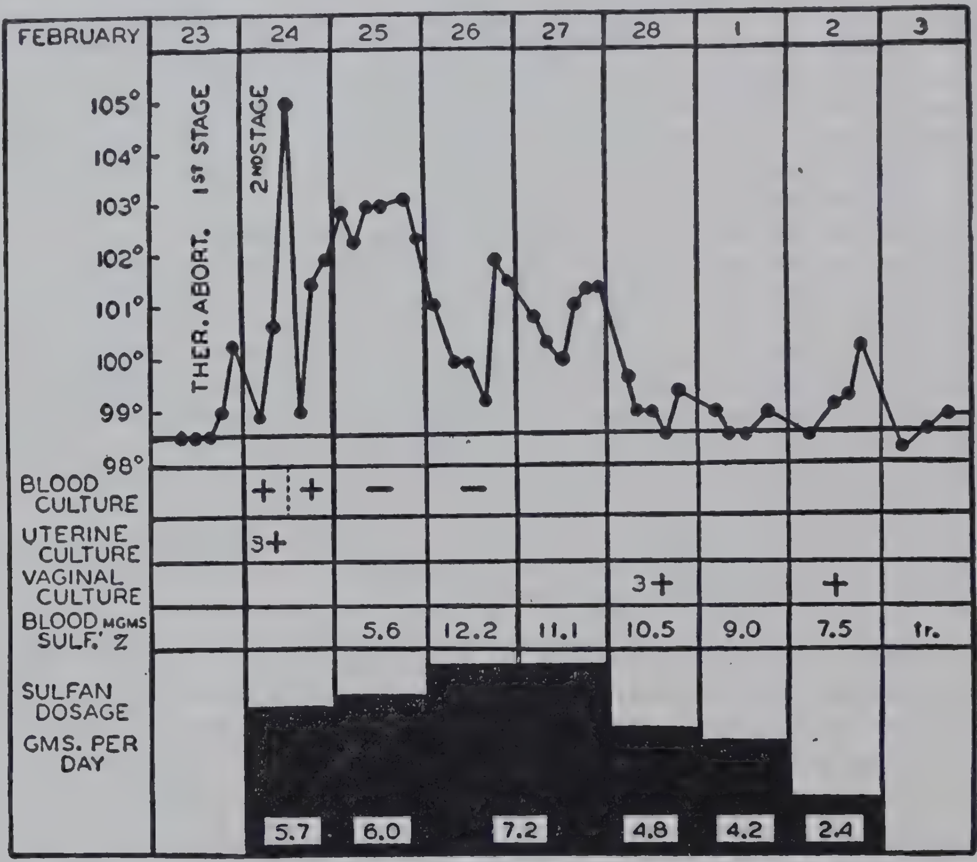

FIGURE 98. *Clinical efficacy of sulfanilamide therapy in puerperal infection due to Cl. welchii.*

White woman, aged 27, third month of pregnancy, therapeutic abortion performed because of long-standing hypochromic microcytic anemia. Abortion was carried out in two stages with chill, fever and severe lower abdominal pain occurring the day after cervical dilatation and packing of lower uterine cavity. Products of conception were removed with ovum forceps after culture of the uterine contents, and no curettage was attempted. Temperature rose rapidly and blood and urine cultures were found positive for gas bacilli. Patient rapidly became critically ill and prostrate. She was cyanotic, breathed shallowly and responded poorly, and the abdomen was greatly distended and exquisitely tender everywhere to even lightest palpation. Sulfanilamide medication was started and continued as shown; the values for the blood levels of sulfanilamide are also given in the chart. By the end of the second day of therapy, the patient was markedly improved, responded well and was brighter, the abdominal tenderness had greatly diminished and blood taken for culture remained sterile. The further dramatic improvement is as illustrated. Vaginal cultures remained positive for *Cl. welchii* for several days, and the placenta showed evidence of invasion with the organism. The patient was discharged to the medical ward in excellent condition 11 days after the sulfanilamide was started. Complete laboratory tests on the microorganisms isolated from the blood and uterus proved beyond question that the infection was due to *Cl. welchii.* (After Sadusk and Manahan, 1939. Courtesy of *The Journal of the American Medical Association.*)

Therapy consists in the use at the earliest possible moment of massive doses of sulfanilamide designed to give blood levels of 15 mgm per cent. This dosage is continued until at least four days after the temperature has become normal and is then gradually reduced over a period of seven to ten days. Local measures include surgical débridement. Long and Bliss urge that all persons sustaining crushing injuries be given moderate doses of sulfanilamide as a *prophylactic measure* as soon as they are seen. The value of the prophylactic use of sulfanilamide is also emphasized by Johnson (1940) from his experience with the treatment of severely contaminated compound fractures. Johnson believes that sulfanilamide is as important for the proper care of compound fractures as antitetanus serum, and that the drug is a necessary addition to the established essentials of fracture treatment: splinting, surgery, serum, *and sulfanilamide.*

Puerperal infections due to *Clostridium welchii* carry a mortality rate of approximately 85 per cent when no specific therapy is given and about 50 per cent when specific antiserum is employed. Sadusk and Manahan (1939) report two cases of this type of infection occurring after abortion. Both patients had positive blood cultures for the gas bacillus but recovered promptly as a result of intensive sulfanilamide treatment. The clinical course of one of their cases is outlined in Figure 98. Cosgrove and Barry (1940) observed a case of gas bacillus infection of the uterus and blood stream successfully treated after delivery of a stillborn fetus by sulfanilamide and polyvalent gas-bacillus antitoxin.

Undulant Fever. The status of sulfanilamide in the therapy of undulant fever is undetermined but the majority of clinical reports suggest that the drug hastens recovery.

Long and Bliss (1939), from a review of the available literature, record 35 prompt recoveries in a total of 44 patients ill with the disease and treated with sulfanilamide. Only four of the 35 cases relapsed. Their own experience with the drug in undulant fever, however, has not been encouraging, and despite good immediate results after intensive therapy relapses occurred after discontinuance of medication in four of their five cases. Bynum (1939) also reported six cases of undulant fever in which sulfanilamide either failed to cause improvement or in which recurrences were observed after cessation of medication. Nevertheless, because of the favorable results obtained by many and the apparent increase in the titers of Brucella agglutinins and opsonocytophagic index (Welch and coworkers, 1938), sulfanilamide is worth trying. Doses as outlined in Table 54 are usually sufficient and should be given until the temperature is normal for one week, then decreased gradually over a period of two months.

Pneumococcal Infections. Although sulfanilamide has been employed with promising results in pneumococcal infections such as *pneumococcal pneumonia, meningitis, peritonitis, otitis media and mastoiditis,* interest and experimentation concerning its actions in these diseases have waned considerably since the advent of sulfapyridine and sulfathiazole.

In *pneumococcal lobar pneumonia,* sulfanilamide in the hands of certain investigators has given satisfactory results, especially in type III infections. Better results were usually obtained by combining the drug with serum therapy in those cases caused by pneumococcal types for which antisera exist. The availability of sulfapyridine and sulfathiazole makes the use of sulfanilamide in pneumococcal pneumonias unnecessary.

In *pneumococcal meningitis,* sulfanilamide has not proved particularly successful even when given in high dosage, although a number of investigators have reported moderate success with it, especially if combined with type specific antipneumococcal serum. Sulfapyridine appears to be the chemotherapeutic agent of choice in this disease. Sulfapyridine and sulfathiazole are the agents of choice for *pneumococcal peritonitis, otitis media and mastoiditis.*

Miscellaneous Infections. Sulfanilamide has proved of value in a number of miscellaneous infections.

In *staphylococcal infections* other than those of the urogenital tract, sulfanilamide has not shown much promise although a number of reports of success with it have appeared. For example, Thornhill and associates (1939) record the cases of two patients with *Staphylococcus aureus hemolyticus* septicemia who recovered after sulfanilamide therapy. Sulfathiazole, however, appears to offer more hope in staphylococcal infections.

In *chancroid,* sulfanilamide has been employed with considerable success, the lesions healing in from five to ten days and buboes resolving without incision (Hanschell, 1938; Hutchison, 1938; Kornblith and associates, 1938; Kristjansen, 1939). Medication with moderate doses is indicated. For example, Schwartz and Freeman (1940) reported successful results with sulfanilamide in 37 carefully studied and selected cases of chancroid, tissue smears being positive for the *Streptobacillus haemophilus of Ducrey.* The average duration of the disease in the 37 sulfanilamide-treated cases was only half as long (15.7 days) as in the 60 control patients (32 days). The average dose of sulfanilamide employed was three grams daily, continued for approximately two weeks.

In *trachoma,* a number of investigators have reported striking improvement after sulfanilamide therapy (Loe, 1938; Kirk and coworkers, 1938; Harley and associates, 1939; Julianelle and associates, 1939; Spining, 1940; Lee and Rottenstein, 1940). Subjective complaints such as pain, photophobia, lacrimation, discharge, blepharospasm, itchiness, etc. are readily relieved, often within a few days. The pannus, keratitis, granulations of the palpebral conjunctivae, entropion, trichiasis, iritis, and corneal ulcerations improve and may even disappear. Best results are obtained in the acute stages or early in the disease and blindness may be prevented. It is not known whether the disease is cured by sulfanilamide, some authorities believing that the benefit observed depends upon the control of secondary infection by sulfanilamide therapy. Apparently, the drug may cause a disappearance of the trachoma virus as indicated by the failure to demonstrate inclusion bodies and the failure of pooled epithelial scrapings to infect baboons (Richards and associates, 1939). This work requires confirmation. Sulfanilamide is administered in moderate doses for trachoma.

In *lymphopathia venereum,* sulfanilamide has been reported to cause complete symptomatic healing, with closing of fistulas and resolution of the complicating rectal strictures (Gjurić, 1938; Hamilton, 1938; Shaffer and Arnold, 1938; Shropshear, 1938; Marino and coworkers, 1939; Knight and David, 1939; Stein, 1940; and others). Moderate doses appear effective. Apparently sulfanilyl sulfanilate gives similarly satisfactory results (Hebb and coworkers, 1939).

In *actinomycosis,* some degree of success has been reported by several workers as a result of sulfanilamide therapy. The disease may show marked clinical improvement or may only be held in check (Poulton, 1937; Walker, 1938; MacCharles and Kippen, 1939; Miller and Fell, 1939).

In *influenzal meningitis,* therapy with sulfanilamide apparently may promote recovery (Jones, 1937; Folsom and Gerchow, 1938; Young and Moore, 1938). Other investigators. however, have not been impressed with the efficacy of the drug in this infection (Neal, 1938; Long and Bliss, 1939; Sappington and Favorite, 1939; Mackenzie and associates, 1940), and none of the six cases treated with sulfanilamide by Waring (1939) recovered.

In *chronic ulcerative colitis,* sulfanilamide has been reported to cause some improvement, especially in the milder cases, and similar results have been recorded for neoprontosil taken orally (Collins, 1938; Brown, Herrell and Bargen, 1939). Much more evidence is required to establish the value of the sulfonamide drugs in this disorder.

In *pemphigus,* Caro (1938) and Lain and Lamb (1938) reported instances of striking improvement after sulfanilamide therapy, and Long and Bliss (1939) have had a similar experience.

In patients operated on for *acute appendicitis* with *abscess* or with *peritonitis,* Ravdin, Lockwood and Rhoads (1940) have reported a decreased mortality (0.3 per cent) in a series of 286 cases treated with sulfanilamide as compared to a control series (1.4 per cent mortality) of 552 cases.

Infections Unaided by Sulfanilamide. Certain infectious diseases are known to be uninfluenced by sulfanilamide therapy. These include *syphilis, tuberculosis, malaria, typhoid fever* and the *common cold.*

Sulfanilyl Sulfanilamide and Sulfanilyl Dimethyl Sulfanilamide

The history, chemistry and trade names, mechanism of action, preparations, and status of sulfanilyl sulfanilamide and its dimethyl derivative have been discussed. Their use entails the same precautions and contraindications as must be observed for sulfanilamide. The toxic reactions are the same as, but more rare than, those occurring after sulfanilamide, with the important exception that the incidence of peripheral neuritis (page 1031) is much higher, approaching one per cent in some series (Long and Bliss, 1939). Both chemicals have a low aqueous solubility and are therefore poorly absorbed from the intestinal tract. The absorbed fraction is excreted almost entirely in the urine where both the free and conjugated forms are found. Although the drugs have been used for many infections, they seem to have found their chief application in the treatment of gonorrhea, especially on the continent but also to some extent in the United States. (*See* O'Crowley and coworkers, 1939; Shelley, 1939; Wilkie, 1939; Alyea and Daniel, 1939; Vest and Parker, 1940; Roth, 1940.) The status of their use in gonorrhea cannot yet be stated, although the immediate results in both males and females are excellent. However, as shown by Cokkinis and McElligott (1938, 1939) from an analysis of a suitably large series of cases, the percentage of very late relapses as distinct from chemotherapeutic failures and early relapses is much higher following therapy with sulfanilyl dimethyl sulfanilamide (18 per cent) than after therapy with sulfanilamide (7.8 per cent). The optimal dosage for the treatment of gonorrhea has not been determined but most investigators employ three grams daily in divided doses for approximately six days and then smaller amounts for another six day period. The practice of interposing rest periods between six day courses of therapy appears unwise due to the tendency of patients to default on their treatment once the acute symptoms have ceased. The hazard to public health from the resulting increase in the number of asymptomatic carriers is very real. From a consideration of the literature, Long and Bliss (1939) advised that the general employment of these agents in gonorrhea is not yet advisable and that their use be restricted to those patients who have proved resistant to sulfanilamide therapy.

Prontosil and Neoprontosil

The history, chemistry and trade names, preparations and status, and mechanism of action of prontosil and neoprontosil have been discussed. The quantitative aspects of the absorption, fate, excretion and optimal doses of these dyes have not been investigated in man in a manner comparable with that for sulfanilamide and sulfapyridine. Prontosil may be given only by the oral route; neoprontosil, by the oral, subcutaneous or intramuscular route but not intravenously or intrathecally. The skin, mucosae, excreta and urine are colored an orange red by the dyes. The same precautions and contraindications must be observed for their use as for sulfanilamide. Indeed, some authorities believe their therapeutic value has been proved only in the case of infections due to the *beta* hemolytic streptococcus, although numerous clinical reports exist describing their use in many other infections. The discovery that the prontosils act in the body by virtue of the release of sulfanilamide has diverted interest from them. At present, there is no convincing evidence that the prontosils deserve preference or are more effective than sulfanilamide or sulfapyridine in any known clinical condition.

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CHAPTER 59

SULFANILAMIDE AND RELATED SULFONAMIDE DRUGS

IV. SULFAPYRIDINE AND SULFATHIAZOLE

SULFAPYRIDINE

Historical. The discovery of sulfanilamide and the demonstration of its efficacy in the therapy of a number of infectious diseases stimulated the search for related drugs of chemotherapeutic value. The chemistry and status of several of the congeners of sulfanilamide have already been discussed. One of the most promising derivatives obtained is sulfapyridine. In a letter to the *Lancet* for May 28, 1938, Whitby reported his striking results obtained with sulfapyridine (a compound prepared by Ewins and Phillips and first called "M&B 693," and later "Dagenan") in experimental infections in mice due to hemolytic streptococci, meningococci and pneumococci, especially types I, II, V, VII and VIII. Later, Whitby announced favorable effects of sulfapyridine in staphylococcal infections. The compound was soon tried in human pneumonia, Telling and Oliver (1938) recording the cure of an individual seriously ill with type III pneumococcal lobar pneumonia. Numerous experimental and clinical studies immediately followed and within a period of two years a vast amount of information has been gained concerning all phases of the actions of the drug. It must be emphasized, however, that sulfapyridine is a relatively new chemical and time will be needed to sift the rapidly accumulating information and properly to delineate the value and dangers of the drug. The Council on Pharmacy and Chemistry (1939) accepted sulfapyridine for inclusion in N.N.R. and issued several reports (1939, 1940) on the actions, uses, toxicity and status of the drug. For detailed reviews of sulfapyridine, the reader is referred to Long and Bliss (1939), Lord, Robinson and Heffron (1940), and Kolmer (1940).

Action in Vitro Against Bacteria. Soon after the original contribution of Whitby (1938), Fleming (1938) demonstrated that sulfapyridine inhibited the growth *in vitro* of large inocula of pneumococci (type 23) in leukocyte-free human blood, effective concentrations being 1:256,000 to 1:8000. When leukocytes were also present, the drug in a concentration of 1:32,000 actually resulted in the death of the organisms. Similar effects were noted against hemolytic streptococci. Fleming also found that sulfapyridine was more effective than sulfanilamide against hemolytic streptococci and pneumococci (type 15) when tested in whole blood. Bliss and Long (1938) showed that sulfapyridine was a somewhat more effective bacteriostatic agent than sulfanilamide in broth cultures of *E. coli, E. Typhi* and Group B *beta* hemolytic streptococci. The two compounds appeared to be approximately equally active against Group C *beta* hemolytic streptococci and *alpha* streptococci, but were both inactive against Group D *beta* hemolytic streptococci and *Staphylococcus aureus.*

A 1:10,000 concentration of sulfapyridine was found capable of a bactericidal action against hemolytic streptococci and pneumococci (Long and associates, 1939). Strains of pneumococci may differ in their resistance to sulfapyridine (Maclean, Rogers and Fleming, 1939; Long and Bliss, 1939), but susceptible strains are markedly inhibited *in vitro* by a 1:10,000 concentration of the drug. Spring and coworkers (1940) and Bullowa and associates (1940) reported on the activity of sulfapyridine *in vitro* against pneumococci of various types, and both groups of investigators found that the combination of type-specific immune serum plus sulfapyridine was more effective than either agent used separately.

Sulfapyridine also appears to inhibit the *in vitro* growth of *Brucella abortus* (Hamann and Huddleson, 1939). Birkhaug reported that the drug is much more effective than sulfanilamide in inhibiting *in vitro* various strains of *mycobacteria,* and Follis (1940) observed that a concentration of 50 mgm per cent of sulfapyridine had a definite bacteriostatic action *in vitro* on *M. tuberculosis hominis.* Green (1940) could demonstrate little or no effect on the *in vitro* growth of human tubercle bacilli when sulfapyridine was employed in concentrations (1:6000 to 1:10,000) compatible with those obtainable clinically.

Action in Vivo Against Experimental Infections. Whitby (1938) first noted the chemotherapeutic efficacy of sulfapyridine in the treatment of mice experimentally infected with hemolytic streptococci, meningococci and pneumococci (especially in types I, II, III, V, VII and VIII), and later in the same year he reported that the drug was also active in staphylococcal infections. Long and coworkers (1939) substantiated, in the main, the major features of Whitby's work. In mice infected with *Staphylococcus aureus,* sulfapyridine therapy resulted in a much higher percentage of survivals than did sulfanilamide (Bliss and Long, 1939). In experimental infections due to *Friedländer's bacillus* and *Clostridium welchii,* sulfapyridine was also effective in mice (Bliss and associates, 1939), the efficacy of the drug in the former infection being corroborated by Kolmer and Rule (1939). In experimental meningococcal infections in mice, Branham (1940) found that sulfapyridine was approximately 10 times more protective than sulfanilamide but somewhat less regular in its action. It was consistently observed that the combination of serum with sulfapyridine or sulfanilamide gave results far better than with either agent alone.

Powell and Chen (1939) found that sulfapyridine was more effective than sulfanilamide against pneumococcal and staphylococcal (aureus) infections in mice, equally effective against those due to meningococci and streptococci, but inferior against typhoid bacilli. Of the 13 types of pneumococci tested, the drug proved particularly efficacious in infections produced by types I, V, VI, VII, XVIII, XXIV and XXIX. A number of other investigators have reported on the value of sulfapyridine in pneumococcal infections in mice and rabbits. Moreover, Raiziss, Kolmer and Rule (1940) found sulfapyridine to be more effective than any of several sulfonamide derivatives examined in the treatment of rats inoculated intrabronchially with Types I, II and III pneumococci. Gregg and coworkers (1940) demonstrated the efficacy of sulfapyridine in saving dogs with experimental pneumococcal (Type I) lobar pneumonia and Kepl and Gunn (1939) found sulfapyridine to potentiate the action of type-specific antiserum when given early to rats with experimental pneumococcal (Type I) lobar pneumonia. Cooper, Gross and Lewis (1939) showed that sulfapyridine was effective in the peritonitis of mice caused by *E. coli* and *B. proteus* but not by *B. pyocyaneus.*

MacIntosh and Whitby (1939) reported that mice treated for experimental pneumococcal infections with sulfapyridine exhibited no greater immunity upon recovery than that produceable by injection of a similar number of killed pneumococci and concluded that the drug did not stimulate the body defenses nor affect the quality, quantity or speed of production of specific antibodies. They also observed that the bacteriostatic action of sulfapyridine *in vitro* and *in vivo* was manifested only after a definite latent period. In rabbits recovering from experimental pneumococcal infection as a result of sulfapyridine therapy, Levine, Larson and Bieter (1939) noted not only pronounced type-specific immunity but also a distinct species-specific immunity as shown by the protection manifested against infection with heterologous types of pneumococci. Mellon and McKinney (1939), in a study in mice of the nature of the bacteriostatic effect of sulfapyridine on the pneumococcus, concluded that the action is essentially of the nature of a phase-transformation which brings the germs within the range of the immuno-phagocytic defenses of the host, and they regarded these phase changes as being implemented chiefly, but not necessarily solely, by the accumulation of hydrogen peroxide. Several investigators have commented on morphological and capsular changes in pneumococci as a result of sulfapyridine therapy of experimental infections, but Reid (1939) found no effect of the drug on the capsule of pneumococci either *in vivo* or *in vitro* that could be ascertained by capsule staining or by the character of the "quellung" reaction in the presence of immune serum, nor did an increase in phagocytosis of the diplococci occur. Reid suggested that sulfapyridine may owe its beneficial effect to a bacteriostatic action which allows clearing of the infection either by normally developing antibodies or by phagocytosis proceeding at the normal rate.

In guinea pigs infected with *Brucella abortus,* sulfapyridine was observed to have little effect on the course of the infection (Hamann and Huddleson, 1939). However, in experimental brucellosis in mice, Kolmer (1940) found that sulfapyridine was most effective against *Br. abortus,* considerably less so against *Br. melitensis* and ineffective, as far as survival was concerned, against *Br. suis.* Rabbits infected with bovine tubercle bacilli are not protected from tuberculosis by sulfapyridine therapy (Follis and Rich, 1939). However, Feldman and Hinshaw (1939) and Birkhaug (1940) observed that sulfapyridine retarded the development and progress of infection in guinea pigs inoculated with human tubercle bacilli. Powell and Chen (1939) found sulfapyridine without value against *rabic virus* and *influenzal virus* in mice.

Mechanism of Antibacterial Action. So far as can be determined, the action of sulfapyridine on bacteria is similar to that of sulfanilamide, the mechanism of action of which has been presented in detail. The available evidence suggests that sulfapyridine inhibits the growth and invasive power of bacteria to such an extent that the humoral and cellular defenses of the body can cope with the infection. Under certain favorable circumstances, the chemical may have a direct bactericidal effect on susceptible microorganisms, especially pneumococci. Phagocytes are not stimulated, antibody formation is not directly enhanced and toxins are not neutralized by the drug. The immune processes of patients and animals with pneumococcal infections treated with sulfapyridine proceed normally and type specific immunity is developed.

Pharmacological Actions

Sulfapyridine, like sulfanilamide, is devoid of pharmacological actions in the strict sense of the word. The drug has practically no effect on body tissues and functions unless administered in doses far above the therapeutic range. An exception exists in regard to the urinary tract where the conjugated form of the drug, due to its insolubility, may precipitate out and form concrements. With large doses in animals, symptoms of poisoning may develop, but these do not necessarily represent the toxic effects seen clinically in patients inasmuch as some of the more serious forms of intoxication are not reproducible experimentally. Moderately large amounts (0.5 to 1.0 gram per kg) administered to dogs for two to seven weeks produce no significant changes in red or white blood cells, hemoglobin, acid-base balance or body weight (Powell and Chen, 1939).

The fatal dose of sulfapyridine appears deceptively high when the drug is administered by mouth, and Wien (1938) concluded that sulfapyridine was only one-quarter as toxic as sulfanilamide. Powell and Chen found the L.D.$_{50}$ for sulfanilamide in mice to be approximately five grams per kg whereas this species tolerates doses of 34 grams per kg of sulfapyridine. They emphasize, however, that the apparently greater safety of sulfapyridine arises from the fact that the drug is poorly soluble and escapes intestinal absorption in varying degree. The inability to establish a true lethal dose of the drug by oral administration was also reported by Long and associates (1939). On the other hand, when absorption is assured by administration of the soluble sodium salt, sulfapyridine proves to be more toxic than sulfanilamide (Marshall and coworkers, 1938; Marshall and Litchfield, 1939).

Chemistry and Preparations. Chemically, sulfapyridine is 2-sulfanilyl aminopyridine. Its structural formula is given in Table 52. The drug occurs as a white, odorless, practically tasteless, crystalline powder. Sulfapyridine is only $\frac{1}{30}$ as soluble as sulfanilamide, being soluble to the extent of approximately 0.03 per cent in water at 20 C., and 0.15 per cent at body temperature, giving a solution which is neutral to litmus. Sulfapyridine is also soluble to the extent of 0.25 per cent in 95 per cent alcohol. It forms water-soluble salts with strong bases or mineral acids.

Sulfapyridine is not an official drug (being patented), but is accepted by the Council for inclusion in N.N.R. *Sodium Sulfapyridine* is also included in N.N.R. and is available for the preparation of solutions to be administered intravenously. It is a white, odorless, practically tasteless, crystalline powder, highly soluble in water (75 grams in 100 cc) to yield solutions which are very alkaline (pH 10.4 to 11.0). The distribution and sale of both sulfapyridine and sodium sulfapyridine are under the regulation of the Federal Food and Drug Administration.

The procedure for the chemical determination of sulfapyridine in body fluids is the same as that for sulfanilamide and has been outlined on page 1019.

Absorption, Fate and Excretion. *Absorption.* Due to its relative insolubility, sulfapyridine is absorbed from the intestinal tract at a much slower rate than sulfanilamide (Marshall and coworkers, 1938; Long and Feinstone, 1939; Stokinger, 1939; Powell and Chen, 1939; Brown and associates, 1939; and others). As a result, a comparative study of the blood after the oral administration of equimolecular doses of sulfanilamide and sulfapyridine reveals that the blood level of sulfapyridine rises much more slowly and does not attain as high a peak as that of sulfanilamide. The incomplete absorption of sulfapyridine is also shown by the presence of the drug in the feces (Brown and coworkers, 1939) and by its lower percentage excretion in the urine as compared with sulfanilamide. The extent of intestinal absorption varies greatly with the individual, showing no relation to the size of the dose.

Fate and Distribution in the Body. Within one-half hour after the ingestion of sulfapyridine, the drug can usually be detected in the blood. Due to its slow absorption, however, peak blood levels are not reached until four to six hours after administration of a single oral dose, and the blood level falls less rapidly than is the case with sulfanilamide.

Like sulfanilamide, the pyridine derivative is acetylated in the human body. The amount acetylated, however, is variable, unpredictable and tends to be considerably higher than is the case with sulfanilamide, so that from 15 to 75 per cent or more of the drug may be present as the therapeutically inactive conjugated form. In general, about 50 per cent of the drug is acetylated in man. It has been noted that the percentage of acetylation increases with the duration of sojourn of the drug in the body, and the conjugated fraction of the drug has therefore been noted to rise sharply in patients with impaired renal function (Brown and coworkers, 1939). Due to variations in absorption and acetylation, an accurate prediction of the dosage necessary for maintaining optimal blood levels of the active free sulfapyridine is difficult and frequent blood determinations are therefore necessary.

Sulfapyridine distributes itself in all the body fluids in a manner similar to sulfanilamide (Marshall and Litchfield, 1939; Chinn and Bellows, 1940; and others). The rate of diffusion of acetylsulfapyridine, however, is slower than that of the free form, and therefore the ratio of free to conjugated sulfapyridine is likely to be higher in the cerebrospinal fluid, for example, than in the blood (Brown and coworkers, 1939). Concentrations of the drug in the various body secretions, transudates and exudates parallel those found in the blood, tending to be slightly lower. Barnett and associates (1939), however, always found the sulfapyridine concentration in pleural exudates to be at least equal to that in the blood.* The concentration in the spinal fluid is from 60 to 80 per cent of that found in the blood. Sulfapyridine enters the fetal circulation from the maternal blood.

Excretion. The main channel for excretion of sulfapyridine is through the kidneys. Although the drug starts to appear in the urine shortly after its oral ingestion, the rate of excretion is considerably below that for sulfanilamide. The main portion of a single dose is eliminated within the first 24 hours, but excretion continues for 50 to 90 hours (Figure 99). Cumulative toxicity may therefore occur from continued medication or improper spacing of doses, and considerable caution is required in patients with impaired renal function. Man excretes about 60 per cent (40 to 80 per cent) of the drug taken by mouth as compared with approximately 95 per cent of sulfanilamide. This is undoubtedly a reflection of incomplete intestinal absorption. Water diuresis hastens urinary excretion of

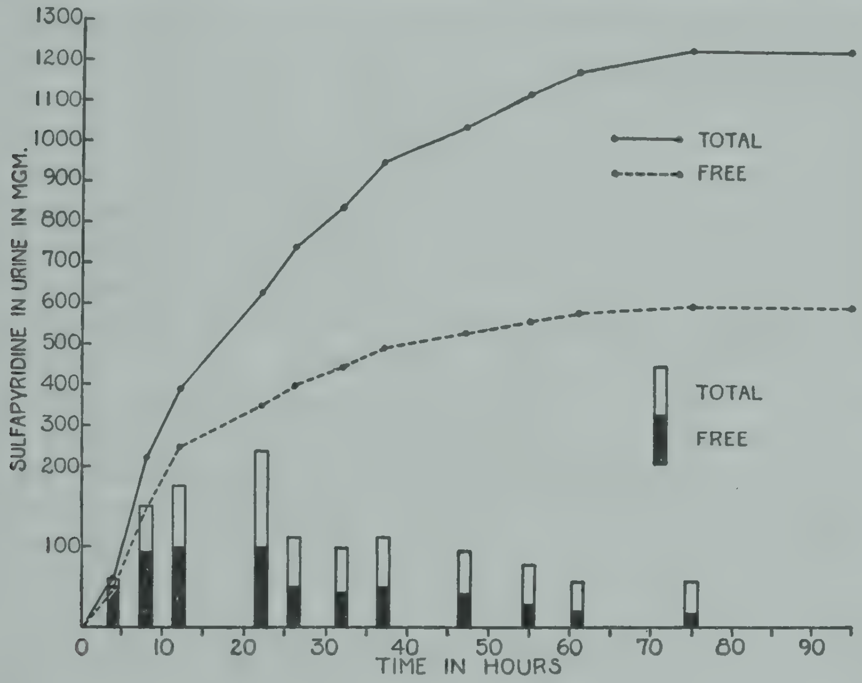

FIGURE 99. *Urinary excretion of sulfapyridine in man.*

A normal young man weighing 82 kg was given by mouth at zero time two grams of sulfapyridine suspended in water. The rate of excretion of free and total sulfapyridine in the urine is shown in two ways. The continuous and broken lines indicate the entire amounts of total and free sulfapyridine, respectively, excreted up to any given hour. The vertical columns indicate the increments of drug excreted in the urine collected at intervals and pooled for convenience of determination. For example, at the 22nd hour is shown the amount of drug excreted during the previous 10 hours. The clear section of the vertical columns represents the acetylated fraction of the drug. Observe the change in scale along the ordinate. Note that the rate of excretion is slower than for sulfanilamide. Although approximately 75 per cent of the excretion occurs within the first 36 hours, appreciable elimination continues during the next 36 hours or more, and the percentage of conjugated drug increases with time. The total amount of drug excreted in the urine is only 62 per cent of that ingested, a reflection of poor intestinal absorption of sulfapyridine, and the acetylated fraction comprises 46 per cent of the total amount excreted. After Powell and Chen, 1939. Courtesy of the *Journal of Pharmacology and Experimental Therapeutics.*)

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* Long and Wood (1939), however, have pointed out that excessively high concentrations of sulfonamide drugs reported in pleural and other exudates may be caused by the use of procaine as a local anesthetic, this and related local anesthetics giving a color reaction quite similar to that of sulfonamide drugs.

sulfapyridine, as it does in the case of sulfanilamide. Extrarenal channels eliminate negligible amounts of the drug. The percentage of conjugated sulfapyridine found in the urine is variable but usually comprises about one-half or more of the total amount present. It has been chemically identified as acetylsulfapyridine (Marshall and coworkers, 1938; Ratish and associates, 1939; Baines and Wien, 1939; Stokinger, 1939). As excretion continues, the acetylated fraction of the compound tends to increase in amount. Acetylsulfapyridine is even more insoluble than the free form and tends to precipitate out in the urinary tract. This may result in untoward effects.

Sulfapyridine is also excreted in small amounts through the same channels discussed under sulfanilamide.

Effective Blood Levels. The optimal blood level of sulfapyridine depends on the type and severity of infection being treated. For example, patients severely ill with pneumococcal lobar pneumonia and bacteremia require, as a rule, from seven to 10 mgm per cent of free sulfapyridine in the blood, whereas in moderately ill patients a blood level of four to six mgm per cent is adequate. On the other hand, in severe staphylococcal septicemia a blood concentration of free sulfapyridine of 10 to 12 mgm per cent or over may be desirable. The therapeutic results obtained, however, cannot be too closely correlated with the blood levels of the drug, and more information is required to determine the optimal concentrations (Flippin and associates, 1939; Blake and Haviland, 1939).

The blood level cannot be predicted from any particular scheme of dosage adopted, and the amount of drug administered can give only an approximate indication of the blood concentration of free sulfapyridine to be expected (Figure 100). This is due, as stated previously, to variations in three factors—rate of intestinal absorption, degree of acetylation and speed of renal elimination. For this reason, frequent colorimetric determinations of the blood level are advisable. An increased fluid intake tends to lower the concentration of sulfapyridine in the blood due to more rapid renal elimination. A low or falling blood level of free sulfapyridine after the second day of therapy should not be considered an indication for increasing the dosage unless the total amount of the drug in the blood is also known. A low or falling level of the free compound due to a high or increasing degree of acetylation constitutes a warning signal, and an increase in the dose may result in hematuria due to the large amount of acetylsulfapyridine in the urine (Blake and Haviland, 1939).

Routes of Administration. *Oral.* Whenever possible, sulfapyridine should be given by the oral route, in capsule or tablet form. If the tablets are first crushed well and given suspended in several ounces of water, milk or fruit juice, absorption is probably facilitated. The drug may be administered through a nasal catheter into the duodenum if nausea and vomiting occur. The necessity for parenteral administration of the drug arises more frequently, however, than is the case with sulfanilamide. This is due chiefly to two factors—poor intestinal absorption of sulfapyridine with resulting difficulty in obtaining optimal blood levels and the more frequent occurrence of severe grades of nausea and vomiting, making oral therapy difficult or impossible. Consequently, technics have been developed to administer sulfapyridine by other routes. A major difficulty encountered is the low water solubility of sulfapyridine, and therefore the highly soluble sodium salt has been employed for parenteral therapy.

Subcutaneous Administration. Blake and Haviland (1939) and Haviland and Blake (1940) reported on the successful use of sulfapyridine itself administered by the subcutaneous route. At body temperature, a sufficient amount of the drug remains in solution to allow proper doses to be given without employing inordinately large volumes of fluid. The technic devised by these investigators is to administer two grams of sulfapyridine in 1500 cc of isotonic sodium chloride solution (0.133 per cent concentration), in 1000 cc of five per cent glucose solution or in a mixture of 500 cc each of five per cent glucose and isotonic sodium chloride solutions (0.2 per cent concentration). Before the drug is added, the solutions are sterilized by boiling and then removed from the burner. When bubbling has ceased, 2.0 grams of pure sulfapyridine powder (not tablets) are added for each 1500 cc of saline solution or each 1000 cc of glucose or glucose-saline solution. Solution of the drug is hastened by stirring with a sterile glass rod, and the mixture is allowed to cool to body temperature before injecting it. Solutions should be freshly prepared each day but may be kept for at least several hours at room temperature. Storage in the icebox will precipitate the sulfapyridine out of solution.

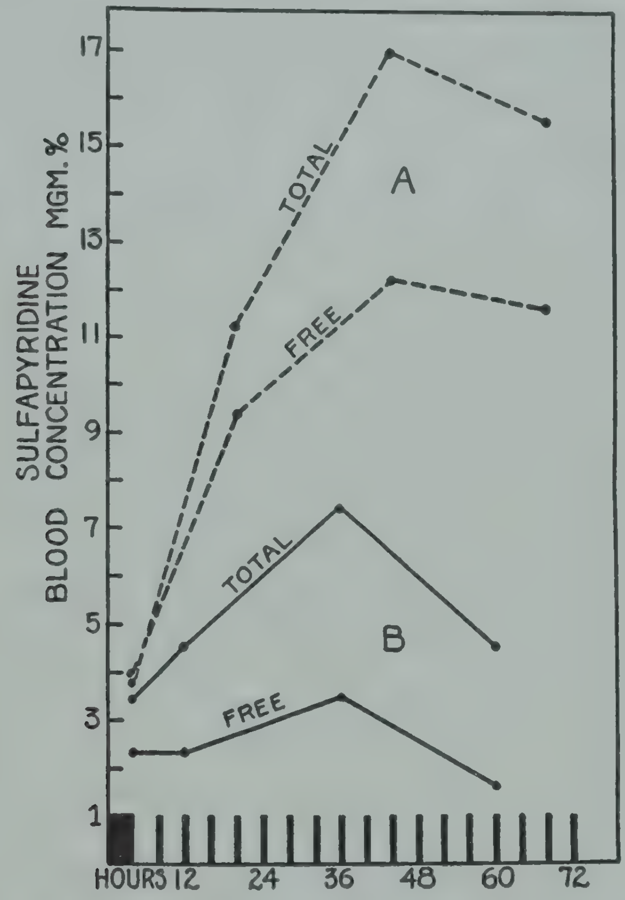


Figure 100. *Variations in blood levels and degree of acetylation of sulfapyridine.*

Both patients, *A* and *B*, received identical amounts of sulfapyridine. The vertical black columns represent one gram doses of sulfapyridine by mouth every four hours. The solid black block in the lower left corner indicates initial therapy with one gram each hour by mouth for the first four hours. Patient *A* (broken line) responded with high blood levels of both free and total sulfapyridine, the conjugated fraction at the peak of the curve comprising 36 per cent of the total. Patient *B* (solid line) responded with a relatively low blood level of the drug, the acetylated fraction at the height of the curve amounting to 53 per cent of the total. Variations in blood levels of total sulfapyridine are reflections of differences in rapidity and completeness of intestinal absorption. (After Blake and Haviland, 1939. Courtesy of *The Connecticut State Medical Journal.*)

The technic of administration is that for any hypodermoclysis. Blake and

Haviland found that two clyses daily at twelve hour intervals (total of four grams of sulfapyridine) are usually adequate for maintenance of proper blood levels and satisfactory therapeutic effects. No untoward responses either local or general were observed as a result of this route of administration. The solutions described may also be given *intravenously*. When it is necessary rapidly to establish an adequate blood concentration of the drug, an initial intravenous injection of 2.0 grams may be given, followed by the same dose by hypodermoclysis. Blake and Haviland are inclined to believe that the aforementioned solutions have an advantage over sodium sulfapyridine solutions in that they can be given both by vein and subcutaneously, they do not cause tissue injury, and they supply water and electrolytes to febrile patients.

Sodium sulfapyridine has also been administered by hypodermoclysis. In 50 patients with pneumococcal pneumonia, Taplin and associates (1940) reported the successful use of 0.3 to 0.7 per cent sodium sulfapyridine in physiological sodium chloride solution, given subcutaneously at the rate of 200 to 300 cc per hour. Despite the high alkalinity of the solution, no local reactions were observed.

Intramuscular Injection. Suspensions of sulfapyridine in oil have been used for intramuscular or subcutaneous injection (Whitby, 1938; Barber, 1938; Lloyd, Erskine and Johnson, 1938), but are not generally recommended because of the rather slow absorption which occurs and the inability rapidly to lower the blood level should toxic effects appear (Long, 1939). The intramuscular injection of very strong solutions of the sodium salt of sulfapyridine was reported by Gaisford, Evans and Whitelaw (1939) who employed a 33⅓ per cent aqueous solution (one gram in three cc). The single dose is three cc, the injection being made deeply into the muscle and *not subcutaneously,* because local necrosis and ulceration are likely to occur due to the high alkalinity of the solution. Apparently pain is not objectionable, and both absorption and excretion of the drug take place more rapidly than after oral administration. The investigators cited suggest that the injection of one gram (in adults) may be made every four hours and repeated from four to six times, oral therapy then being instituted if possible.

Intravenous Injection. The intravenous administration of solutions of the sodium salt of sulfapyridine has also been used to advantage when oral therapy is inadequate or impossible due to nausea or vomiting. The technic generally employed is that suggested by Marshall and Long (1939), and numerous clinical reports testify to its therapeutic value. A five per cent solution of the sodium salt in sterile distilled water is practically isotonic. Sodium sulfapyridine is unstable to heat and its solutions cannot be boiled. The alkalinity of the solution (pH 10.8) necessitates that the injection be made *very slowly* and that care be exercised to avoid any extravasation. The initial dose usually given is 0.05 gram per kg of body weight (0.06 gram per kg of the sodium salt with one mole of water of crystallization). This amounts to one cc of the five per cent solution per kg of body weight. The solution is infused slowly (five cc per minute) over a period of 10 to 15 minutes. Almost immediate establishment of effective blood levels of the drug (five to eight mgm per cent) is possible by the use of this route, and distribution of the chemical between the blood and tissues is nearly complete in from five to ten minutes after the injection is terminated. The blood level is quite well sustained and does not start to fall appreciably before an hour or more has passed. Severely ill patients may receive one or rarely two subsequent injections at six to eight hour intervals, and oral sulfapyridine in the dose of one gram every four hours is started at the time of intravenous therapy. Untoward effects from properly prepared and injected solutions of sodium sulfapyridine apparently do not occur except for occasional vomiting or chill during or immediately after the injection.

Sulfapyridine itself may be given intravenously in solution in saline or glucose by employing the technic of Blake and Haviland previously described.

Larger volumes of fluid must be employed due to the relatively low solubility of sulfapyridine, and one to one and one-half liters of solution must be injected in order to administer two grams of drug.

Rectal Administration. Quantitative data concerning the rectal absorption of sulfapyridine and sodium sulfapyridine are incomplete. Barnett and coworkers (1939) reported that successful therapeutic results in infants followed the use of a two per cent solution of the sodium salt given as a retention enema, that absorption was rapid and that adequate blood levels were maintained without difficulty. Sulfapyridine has also been administered in suspension as a retention enema, generally with a little gum acacia or starch. Whittemore and associates (1940) treated 14 patients with pneumococcal pneumonia using a suspension of sulfapyridine in a 1.0 per cent solution of sodium bicarbonate. After a cleansing enema, an initial dose of six grams in 100 cc was given, followed at four hour intervals by doses of two or three grams. The clinical response, though uniformly satisfactory, was slower and the blood levels lower than when the oral or intravenous route was employed. Rectal irritation did not occur and nausea and vomiting were noted in only one patient.

Dosage. As in the case of sulfanilamide, the dose of sulfapyridine cannot be stated categorically and depends on many factors. Chief among these are the nature and severity of the infection, the degree to which intestinal absorption and renal excretion allow adequate blood levels to be reached, the percentage of the acetylated fraction, the functional status of the kidneys, and the occurrence of untoward symptoms which necessitate reduction in dosage or special routes of administration. Determinations of the blood levels of free and total sulfapyridine are essential for safe and adequate therapy. The following suggestions as to dosage are to be considered only as approximations. (*See* Marshall and Long, 1939; Blake and Haviland, 1939; Long and Bliss, 1939; N.N.R., 1940.)

In adults with severe infections (*e.g.*, pneumococcal lobar pneumonia) in whom it is desirable quickly to reach and maintain blood levels of free sulfapyridine of six to 10 mgm per cent for two or three days or more, an initial dose of four grams may be given orally or one gram administered each hour for four doses. This is then followed by one gram every four hours day and night until the temperature has remained normal for 48 hours or more. The dose may then be reduced to 1.0 gram every six hours until recovery has progressed for three or four more days. Doses of 0.5 gram four times daily may then be used and continued until the patient is partially ambulatory. Too rapid withdrawal of the drug may allow recurrence of the infections. Adults with less severe infections are given proportionately smaller doses designed to obtain blood levels of four to six mgm per cent of sulfapyridine. In general, patients receiving six grams daily show blood concentrations of total sulfapyridine averaging between eight and 12 mgm per cent; three grams daily, between four and six mgm per cent. These levels are only approximate, however, and considerable individual variation exists. For example, Flippin and associates (1939) noted in 100 patients on the identical dose schedule that the free sulfapyridine varied from one to 18 mgm per cent, and Plummer and Ensworth (1939) in their series of 270 patients on the same routine dosage scheme observed that the free sulfapyridine levels in the blood varied from traces to 25 mgm per cent.

Children and infants with severe infections may be given an initial dose of 0.5 to 2.0 grams, depending on body weight, and then 0.25 to 0.5 gram every four to six hours until the acute phase has subsided and the temperature has been normal for 48 hours or longer. The doses are then reduced but not discontinued until recovery is well under way. During the acute stage of the infection, the total daily dose should be from 0.1 to 0.2 gram per kg of body weight.

The doses employed when subcutaneous or intravenous administration is required have been outlined. In patients with severe infections who do not manifest within 24 hours an adequate clinical response to orally administered sulfapyridine or in whom the blood concentration of the free fraction remains under four mgm per cent, an intravenous or subcutaneous injection of the drug may be indicated, the oral doses being continued according to schedule (Long and Wood, 1939).

Clinical Toxicology of Sulfapyridine

The use of sulfapyridine requires the same numerous precautions as have been outlined in detail for sulfanilamide. The pyridine derivative appears to cause all the toxic reactions produced by sulfanilamide, although the absolute incidence of these varies somewhat. In addition, the slower rate of excretion of sulfapyridine provides a more ready basis for cumulative poisoning, and the insolubility of the acetylated fraction results in its precipitation in the urinary tract with resulting untoward effects. Experimental studies in animals and clinical observations indicate that sulfapyridine is more toxic than sulfanilamide. Treatment of the toxic reactions to sulfapyridine is the same as described for sulfanilamide. In Table 55, compiled by Long and coworkers (1940), are given the incidence, time of appearance, and clinical significance of the toxic manifestations of sulfapyridine as compared to those appearing after sulfanilamide and sulfathiazole. Similar data have been presented by Brown and associates (1940).

Nausea and Vomiting. Nausea and vomiting are much more frequent after sulfapyridine than after sulfanilamide, and occur after both oral and parenteral administration of the drug. Occasionally, vomiting may be sufficiently severe to interfere with the oral use of sulfapyridine. Also, it may strain abdominal wounds and surgical incisions in patients with postoperative pneumonia. Plummer and Ensworth (1939) noted nausea in 52 per cent of 323 patients, vomiting in 40 per cent and severe vomiting in 10 per cent. Flippin and associates (1939) observed nausea in 56 per cent of 100 cases, troublesome vomiting in 30 per cent and severe vomiting in 10 per cent. Finland and coworkers (1939) reported that approximately two-thirds of their 342 patients were nauseated by sulfapyridine, and Pepper and coworkers likewise noted a high incidence in a series of 400 patients. Blake and Haviland (1939) reported that 60 of 128 sulfapyridine-treated patients experienced nausea and vomiting, the untoward effects being quite severe in one-third of these. Children are less likely to develop the symptoms than are adults.

Nausea and vomiting begin within a few hours after the initial dose and usually continue for several days. Often, however, the emesis may subside despite continuation of therapy. The patient may feel so wretched due to the nausea and vomiting that the physician may be dissuaded from continuing needed treatment or the clinical improvement produced by sulfapyridine therapy may be obscured. This prompted Hinshaw (1939) to overstate the case by warning physicians employing sulfapyridine in severe infections to "watch the chart and not the patient."

Many suggestions have been made concerning methods to lessen or prevent nausea and vomiting, but none has been successful. The symptoms are apparently neither of gastro-intestinal nor central origin and proof of this has been obtained by Sadusk and Hirshfeld (1940) who noted vomiting movements in gastrectomized and eviscerated animals within a short period (15 to 20 minutes) after the intravenous injection of the drug. Both the operated and intact animals were affected at the same blood level (about 25 to 30 mgm per cent). In addition, dogs did not vomit when a solution of sulfapyridine was applied directly to the emetic center in the floor of the fourth ventricle. This phenomenon is reminiscent of the problem involved in digitalis emesis (page 519). Central nervous system sedatives such as chloral hydrate and barbiturates may diminish the sensitivity of the vomiting center. If the severity of the disease being treated demands continuation of sulfapyridine, intravenous or subcutaneous administration may be necessary in order to establish and maintain effective blood concentrations of the drug. The incidence of nausea and vomiting is not decreased by parenteral use of sulfapyridine.

Cyanosis. Cyanosis is less frequent and less intense after sulfapyridine than after sulfanilamide. This may possibly be explained by the fact that the drug is less easily oxidized to substances capable of producing methemoglobinemia, and exposure of the drug to ultraviolet light does not produce colored products (Vigness, Watson and Spink, 1940). When cyanosis does occur, it is due to methemoglobinemia and, if necessary, can be relieved by methylene blue in a manner already described (page 1032) (Campbell and Morgan, 1939; Barnett and coworkers, 1939; Harris and Michel, 1939).

Drug Fever and Skin Rashes. The incidence of *drug fever* is about as high for sulfapyridine as for sulfanilamide. Blake and Haviland (1939) reported the occurrence of fever associated with a more or less extensive morbilliform, maculopapular rash in approximately 10 per cent of their series, and Long and coworkers (1940) observed fever in four per cent and rash in two per cent of 297 patients receiving sulfapyridine. As is true for sulfanilamide, the fever bears no relation to age, dose of drug, duration of treatment, type of infection, etc., and is characterized by the fact that it is likely to occur about one week after medication is started. Drug fever necessitates the cessation of sulfapyridine and the administration of abundant fluids.

Skin eruptions due to sulfapyridine occur with the same frequency as is noted with sulfanilamide (Table 55). They may take any of the forms described for sulfanilamide and have a similar significance.

Urinary Tract Complications. The excretion of acetylsulfapyridine in high concentration in the urine is the basis for a number of untoward reactions due to the poor solubility of the conjugated compound. Crystals of acetylsulfapyridine precipitate out of the urine and lodge in the renal tubules or pelves, ureters and bladder. They may even form impactions or stones, and calcium may be deposited about them. Renal function is impaired and cases of complete anuria and death have been reported. These complications represent a most serious toxic effect of the drug, necessitate careful daily microscopic examination of the urine and cessation of therapy at the first indication of serious urinary symptoms. The untoward effects then usually subside very rapidly without residual injury. Cystoscopic manipulation and ureteral lavage may be necessary at times to loosen aggregations of acetylsulfapyridine obstructing urine flow.

Gross as well as microscopic hematuria in patients receiving sulfapyridine has been reported by a number of investigators. Although macroscopic hematuria is an absolute indication for stopping the drug, the problem is more difficult in patients showing only microscopic hematuria and who are seriously ill with an infection requiring sulfapyridine. Long and Wood (1939) did not discontinue therapy when 10 to 20 red blood cells per high power field appeared in the urine if the clinical condition of the patient indicated that sulfapyridine should be continued. In those with microscopic hematuria, symptoms are usually mild, but the more severe cases are characterized by grossly bloody urine, fever, costovertebral tenderness and renal colic.

Blake and Haviland (1939) observed acute hematuria in eight of 128 patients with pneumonia, the blood usually appearing in the urine on the third or fourth day of sulfapyridine therapy. Southworth and Cooke (1939) reported three cases of hematuria (one with gross blood) due to sulfapyridine. In two of the patients, severe abdominal pain of renal or ureteral origin was present, whereas the pain in one instance simulated that of acute appendicitis. Nitrogen retention also occurred. Nissen and Roesgaard (1939) demonstrated hematuria in 15 of 41 patients on sulfapyridine therapy, and in five of these the hematuria was macroscopic. Renal colic and anuria developed in only one instance. Long and Wood (1939) were able to demonstrate acetylsulfapyridine crystals in the urine of practically all of their patients receiving sulfapyridine for the treatment of pneumonia. Pepper and coworkers (1939) state that seven per cent of 381 patients whose urines were examined during sulfapyridine medication for pneumonia revealed hematuria, whereas the incidence of hematuria in pneumonia patients not on chemotherapy is only four per cent. Antopol (1940) observed microscopic hematuria in 16 of 40 patients receiving sulfapyridine for pneumococcal pneumonia. Plummer and Ensworth (1939) recorded temporary nitrogen retention in three of 323 patients receiving sulfapyridine, ureteral stone in two and hematuria without proved stone in four. Tsao and coworkers (1939) noted five in a group of 40 children receiving sulfapyridine who developed hematuria, and one patient died in uremia from complete urinary obstruction verified at autopsy. Carroll, Shea and Pike (1940) observed a patient in whom complete urinary obstruction occurred due to acetylsulfapyridine and a fatal outcome was averted only by inserting ureteral catheters and lavaging the urinary tract.

Finland and coworkers (1939), in a series of 342 cases, observed two instances of impaired renal function with nitrogen retention. Both patients died. One of the 70 cases reported by Smith and Needles (1939) developed anuria and died of an extension of a pneumonia. An acute toxic nephritis which was attributed to the drug was found at autopsy. MacLeod (1939) recorded that following sulfapyridine there may occur depression of renal function in the absence of symptoms or hematuria, as shown by an elevation of the blood non-protein nitrogen and a depression of the urea clearance. He also describes two patients with acute hemorrhagic nephritis developing during sulfapyridine therapy for pneumonia.

Experiments by several investigators have shown the development of uroliths in animals after administration of sulfapyridine for varying periods of time. For example, Antopol and Robinson (1940) observed concretions of acetylsulfapyridine in the urinary tract of rats, rabbits and monkeys which were fed sulfapyridine for 10 days, and smaller doses of sodium sulfapyridine produced identical lesions. Similar results were obtained with sodium sulfapyridine by Molitor and Robinson (1939) who noted that single large doses may also produce uroliths. The concrements in the urinary tract permit penetration by roentgen ray when the routine technic is used (Brown and coworkers, 1940), but they can act as nuclei about which calcium may be deposited. Hematuria, ureteral dilatation, pyelitis and loss of renal substance may occur. In rats cured of pneumococcal infections by sulfapyridine, Gross and coworkers (1939) noted enlargement and softening of the kidneys, dilated pelves and ureters and deposition in the urinary tract of crystalline, spiculated concretions and sand composed chiefly of the acetylated form of the drug.

Agranulocytosis. Leukopenia and agranulocytosis occur after sulfapyridine. Several deaths have resulted from this complication (Rosenthal and Vogel, 1939; Dolgopol and Hobart, 1939; Morgan and Detweiler, 1939; Finland and coworkers, 1939; Long and Wood, 1939). Blake and Haviland (1939) observed four instances of granulocytopenia in 128 sulfapyridine-treated patients with pneumonia, one case being fatal, and Brown and associates (1940) observed three instances in 100 patients given sulfapyridine. The incidence reported by Long and coworkers (1940) is considerably lower (Table 55). The total and differential white blood cell counts should be performed daily on all patients receiving sulfapyridine, and the drug should be stopped and fluids forced at the first suggestion of neutropenia.

Acute Hemolytic Anemia. Mild to moderate degrees of anemia have been observed to occur gradually during the course of sulfapyridine therapy and require no special treatment. As in the case of sulfanilamide, the anemia is due to increased blood destruction as a result of hemolysis. The hemolysis escapes detection unless special methods are used. Thus, Erf and MacLeod (1940) noted a one and one-half to five-fold increase in the excretion of urobilinogen in the stools and urine of eight of 20 patients on sulfapyridine therapy. However, the investigations of Rimington (1940) indicate that sulfapyridine is no more toxic than sulfanilamide with respect to increasing the excretion of urinary porphyrins. Acute hemolytic anemia, nevertheless, may develop and this necessitates immediate cessation of medication, forcing of fluids and blood transfusions as outlined under sulfanilamide. Blake and Haviland (1939) noted only one instance of acute hemolytic anemia in their series of 128 patients with pneumonia; Long and Wood (1939) noted two in a series of 108 patients; Flippin and coworkers (1939) observed one instance in 100 pneumonia patients, and Pepper and associates (1939) recorded only one case among 400 sulfapyridine-treated pneumonia patients. MacLeod (1939), on the other hand, observed three instances of acute hemolytic anemia in a series of twenty patients. Individuals on sulfapyridine therapy should have a daily hemoglobin determination and red blood cell count.

Miscellaneous Reactions. Sulfapyridine does not appear to cause disturbances in the *acid-base balance* and there is no reason to administer alkali with it. Mild toxic effects referable to the *central nervous system*, such as headache, malaise, vertigo, excitement, depression, confusion, etc., occur after sulfapyridine and are similar to the symptoms noted after sulfanilamide. A syndrome suggesting a mild attack of encephalitis may occasionally occur (Long and Wood, 1939). *Toxic hepatitis* has also been reported from sulfapyridine therapy, and jaundice may occur unassociated with acute hemolytic anemia. Hepatic dysfunction apparently is somewhat less frequent after sulfapyridine than after sulfanilamide (Watson and Spink, 1940). When sulfapyridine is used in patients with pneumonia, the occurrence of jaundice cannot always be attributed to the drug because the incidence of jaundice in pneumonia is approximately seven per cent.

Therapeutic Uses

Sulfapyridine has had clinical trial in almost every disease for which sulfanilamide therapy has been employed. With the exception of pneumococcal infections, in which sulfapyridine is superior to sulfanilamide, the exact status of the drug cannot be stated. It appears to show some promise as a therapeutic agent in staphylococcal infections and in *Friedländer's bacillus* infections, but the results obtained leave much to be desired. Although good effects have been reported in meningococcal, gonococcal and streptococcal diseases, it remains to be shown whether these are better than those obtainable with sulfanilamide. Should the drug prove superior to sulfanilamide in the therapy of certain infections, it still must be demonstrated that the superiority is of sufficient magnitude to compensate for the greater toxicity of sulfapyridine. A safe procedure would be not to employ sulfapyridine in preference to sulfanilamide unless and until the results with sulfapyridine have been proved without question to be better than could be expected from sulfanilamide.

Precautions and Contraindications. In addition to using sulfapyridine only in diseases where the anticipated results justify its preference over sulfanilamide, certain other precautions and contraindications must be observed. Those outlined for sulfanilamide apply equally to sulfapyridine, in addition to certain others which are based on the specific peculiarities of the latter drug. The only absolute contraindication to the use of sulfapyridine is the previous occurrence of a serious toxic response to it or to sulfanilamide, such as hemolytic anemia, jaundice, agranulocytosis, severe dermatitis or drug fever. In such instances, the patient should be given a small test dose (0.3 gram) and carefully observed for 12 hours for the occurrence of untoward effects, particularly fever, headache, malaise or skin eruption. When renal function is impaired, sulfapyridine must be administered with extreme caution and frequent estimations of the blood concentration of both the free and acetylated fractions of the drug should be made. The incidence of toxic effects is much greater in patients with unnecessarily high blood levels of the drug and in those in whom excessive acetylation occurs (Brown and coworkers, 1939). A falling concentration of free sulfapyridine in the blood does not always signify that an increase in dosage is indicated, because it may be due to an increasing degree of acetylation, in which case an increase in dose may result in acute hematuria or other untoward urinary effects (Blake and Haviland, 1939). Blood and urine examinations should be made daily. When the toxic effects necessitate the cessation of medication, the forcing of fluids will assist in lowering the blood level of sulfapyridine by hastening its renal excretion. Sulfapyridine must be employed with caution in postoperative cases, if the possibility of vomiting should be avoided.

Pneumococcal Infections. Sulfapyridine is most useful in the therapy of pneumococcal infections. The excellent results obtained are far superior to those reported for sulfanilamide. So far as is known, sulfapyridine is equally effective against all the recognized types of pneumococci. It has been successfully employed in many forms of pneumococcal infections, including *pneumonia, septicemia, menigitis, peritonitis, otitis media* and *mastoiditis.*

Pneumonia. A large and ever increasing literature on the use of sulfapyridine in pneumonia has accumulated in the short space of time since Telling and Oliver (1938), acting on the results of Whitby's animal experiments, first reported the successful use of the chemical in the treatment of a patient severely ill with type III pneumococcal lobar pneumonia. The problems raised are many and several more years of clinical experience may be required before adequate answers are available. Only the salient features can be presented and details must be sought in special articles and reviews listed in the references.

The first extensive series of cases to be reported was that of Evans and Gaisford (1938) who treated 100 unselected patients with pneumococcal pneumonia with sulfapyridine and obtained a case mortality figure of eight per cent, as compared with 27 per cent in a control group of 100 patients receiving only symptomatic therapy. Numerous other reports quickly followed. (*See* Pepper and associates, 1939; Blake and Haviland, 1939; Long and Wood, 1939; Finland and coworkers, 1939, 1940; Kilgour, 1939; Schwartz and associates, 1939; Plummer and Ensworth, 1939; Don and coworkers, 1940; Dowling and Abernethy, 1940; Plummer, 1940; Cecil and associates, 1940; Abernethy and associates, 1940; and many others.)

The results obtained with sulfapyridine are uniformly good. For example, Pepper and associates treated 400 patients with typed pneumococcal pneumonia and reported a case mortality rate of seven per cent. Nearly one-half of the cases were due to Types I, II and III. No deaths were believed to have been caused by the drug nor were patients encountered who could not tolerate therapeutic doses. These investigators advanced the opinion that sulfapyridine therapy may be instituted without waiting for typing of the pneumococcus. Blake and Haviland treated 60 patients suffering from pneumococcal lobar pneumonia with sulfapyridine alone, and only three of the series died (five per cent). Three additional deaths occurred in 33 patients in whom sulfapyridine therapy was combined with serum. They concluded that the efficacy of chemotherapy equals that of specific antipneumococcal serum, that the combined use of serum and drug perhaps might best be reserved for advanced cases with extensive consolidation and possibly bacteriemia and that the drug was not of value in "atypical" bronchopneumonias not predominantly of pneumococcic etiology.

Of 270 patients with pneumococcal pneumonia, both typical (lobar) and atypical, treated by Plummer and Ensworth with sulfapyridine, 23 individuals or 8.5 per cent died (excluding 11 deaths occurring within 24 hours). Serum was employed in 102 of the cases but no conclusion was reached as to the value of combined therapy. Finland and associates (1940), from their experience with 1037 cases of pneumococcal pneumonia receiving sulfapyridine and serum alone or combined, or no specific measures, concluded that either chemotherapy or serotherapy is quite effective but that in severe cases, including those with bacteriemia, the combined treatment reduces the mortality more effectively than serum alone. Long and Wood used sulfapyridine, with or without serum, and serum alone in 139 patients with presumptive pneumococcic pneumonia, in 129 of whom pneumococci were obtained from the sputum and identified by specific antisera in 124. The case mortality was 7.2 per cent. In 100 of the cases, sulfapyridine alone was employed. Twelve per cent of these had positive blood cultures, and five developed complications associated with pneumonia. Forty-two per cent had major concurrent diseases, while seven suffered from severe toxic reactions due to sulfapyridine therapy other than those of nausea and vomiting. Two deaths occurred (excluding two patients who died within six hours after the first dose of sulfapyridine), a case mortality of two per cent.

The excellent results obtained by individual investigators are abundantly confirmed by statistical analyses of reports collected from the literature. For example, Plummer (1940) records 996 cases of pneumococcal pneumonia treated with sulfapyridine in

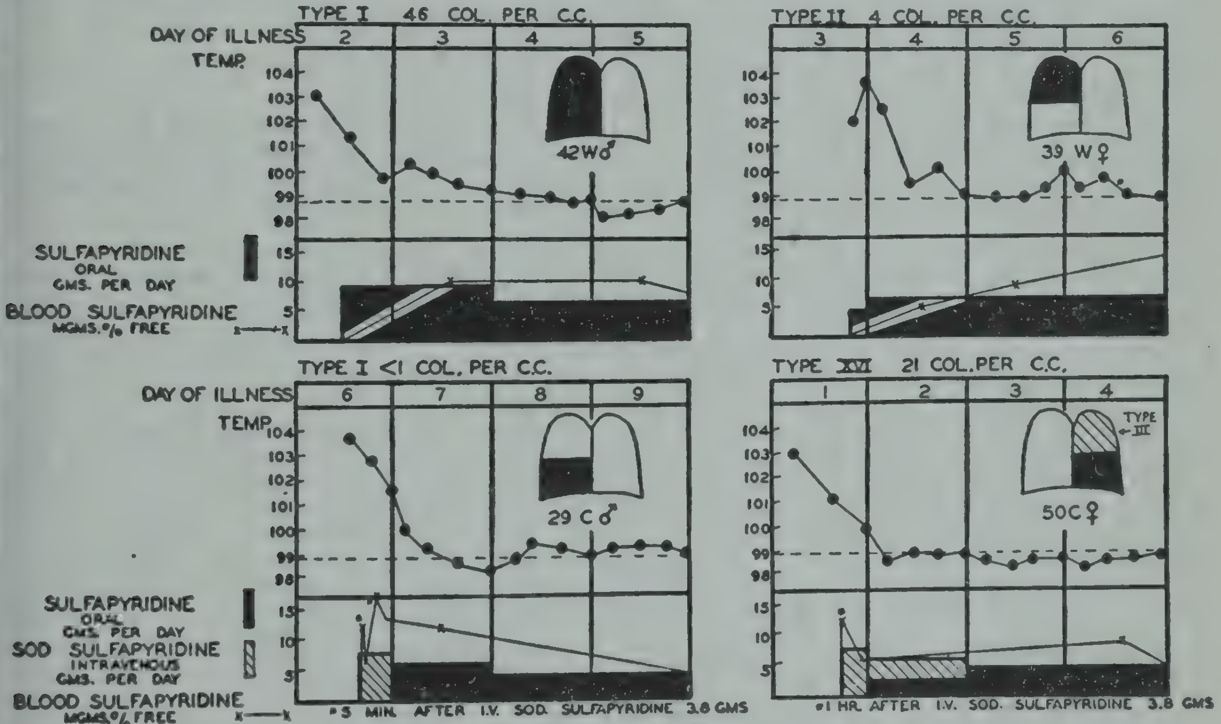


FIGURE 101. *Clinical response to sulfapyridine in four patients with pneumococcal lobar pneumonia and bacteremia.*

The type of pneumococcus and number of colonies per cc of blood are shown at the top of each chart. The areas of pulmonary consolidation are depicted in the inserts. The total daily dose of sulfapyridine by mouth is represented in solid black at the bottom of each chart; the dose of sodium sulfapyridine by vein, in the cross-hatched section. The free sulfapyridine in the blood is shown in mgm per cent, and the asterisks in the two lower charts signify that the blood samples were taken at the stated intervals after intravenous injections of the drug. Note the rapid decline in the temperature and that blood concentrations of more than four mgm per cent of free sulfapyridine were obtained in the four cases within 24 hours. (After Long and Wood, 1939. Courtesy of the *Annals of Internal Medicine.*)

which the mortality rate was 8.5 per cent as compared to 32.8 per cent among 19,000 cases not given specific therapy. In 3005 cases of typed pneumococcal pneumonia given sulfapyridine (data collected by Merck and Company, 1940), the fatality rate was only 6.0 per cent. In 2342 sulfapyridine-treated cases of pneumonia collected from the literature by Lord and associates (1940), the mortality rate was 6.1 per cent. The evidence available indicates that treatment with sulfapyridine reduces the fatality rate of lobar and unspecified pneumonia from approximately 25 per cent to approximately seven per cent; pneumococcal pneumonia, from 25 to 30 per cent to six or seven per cent; Type I pneumococcal pneumonia from the expected 30 per cent to five or six per cent; Type II pneumococcal pneumonia from the expected 40 per cent to approximately five per cent; Type III pneumococcal pneumonia from the expected 45 or 50 per cent to eight or nine per cent (Lord, 1939; Lord, Robinson and Heffron, 1940). In Type III pneumococcal pneumonia, the results obtained with sulfapyridine therapy are distinctly better than those obtainable with serum. Sulfapyridine is not effective in bronchopneumonias unless predominantly pneumococcic in origin.

In *infants* and *children* with pneumonia, even more dramatic responses have been obtained with sulfapyridine than in adults. (*See* Smith and Nemir, 1939; Davies, 1939; Barnett and coworkers, 1939; Hodes and associates, 1939; Friedenwald and Bereston, 1939; Wilson and associates, 1939; Reynolds and Slobody, 1939; Scott, 1940; Christian and coworkers, 1940; and others.) In a combined series of case collected from the literature by Lord and associates (1940), 256 infants and children with pneumonia were treated with sulfapyridine and only six deaths (2.3 per cent) occurred.

Sulfapyridine therapy alone causes a rapid decline in fever and pulse rate, often precipitate in character (Figure 101). The temperature usually becomes normal in from 24 to 48 hours. Resolution of the pneumonic process may occur quickly or slowly over a period of several days. Signs of consolidation may occasionally become more marked even after the fever has disappeared. In many cases, the usual evolution of the pneumonic process in the lungs is not altered by the drug, despite the fall in temperature and general improvement in the patient's condition. Sulfapyridine decreases the incidence of pulmonary extensions and complications of the infection. *Pneumococcal empyema* usually responds to sulfapyridine therapy and repeated thoracenteses.

Adequate dosage is a primary requisite for success and smaller doses may be useless. The drug must be given day and night, even if rest and sleep are disturbed. Nausea and vomiting are to be expected and indicate not cessation of therapy but a shift to parenteral medication. The routes of administration and dosage have been discussed.

The exact *blood level* of sulfapyridine for optimal effects cannot be stated and the numerous studies thus far have failed to establish a definite correlation between blood levels and therapeutic response (Flippin and coworkers, 1939; Blake and Haviland, 1939; Plummer and Ensworth, 1939). It seems, however, that a blood concentration of more than five or six mgm per cent of the free form of the drug is essential for success in the severer grades of infection (Abernethy and coworkers, 1940). If the temperature has not fallen to 101 F. or below (rectal) within 24 hours after institution of chemotherapy and the blood level of free sulfapyridine is less than four mgm per cent, parenteral administration of the drug should be considered (Long and Wood, 1939). In severely ill patients, it is preferable to start therapy by the parenteral route. If a patient fails to respond within 48 hours despite the maintenance of a blood level of free sulfapyridine over four mgm per cent, the use of type-specific antipneumococcal serum is probably indicated (Long and Wood, 1939; Lord, Robinson and Heffron, 1940).

The *duration of treatment* depends on the severity of the infection, the response of the patient, and the development of complications or untoward reactions to the drug. Sulfapyridine should be continued sufficiently long to prevent relapses. As a rule, the drug is not discontinued in the average case until at least after the seventh to ninth day of the pneumonia, at which time protective antibodies will usually have developed.

Effect of Sulfapyridine on the Immunological Processes in Pneumonia. This subject is a matter of considerable interest and importance. Edwards and associates (1939) observed that the immune responses of patients treated with sulfapyridine for pneumococcal pneumonia did not differ from those of untreated patients, as determined by the type-specific and species-specific agglutinins and by the dermal reactivity to type-specific polysaccharides. Wood and Long (1939), in 12 patients with types I, II or III pneumococcal lobar pneumonia treated with sulfapyridine, noted that essential recovery occurred in seven patients before specific antibody could be detected in the serum. Inasmuch as type-specific antibodies are presumed to play an important rôle in the process of recovery from pneumococcal pneumonia following treatment with sulfapyridine, these investigators suggest that the lateness of appearance of circulating antibodies (which may not appear until several days after the temperature has fallen to normal) may be a possible explanation for the relapses which are frequently observed when sulfapyridine therapy is discontinued too soon. The lateness of appearance of specific immunity in patients showing apparent clinical recovery after sulfapyridine therapy is also indicated by the studies of Kneeland and Mulliken (1940) and Fox and coworkers (1940).

It has been known for some time that the body apparently cannot dispose of virulent pneumococci by phagocytosis unless the bacteria are previously sensitized by specific antibody, even killed pneumococci not being ingested by leukocytes without prior sensitization. It seems that sulfapyridine injures the pneumococcus whereas type-specific antibodies fortify the patient's ability to destroy the organism. Finland and associates (1940) observed that the blood of patients undergoing sulfapyridine therapy for pneumococcal pneumonia has a marked bacteriostatic and considerable bactericidal action on the homologous type of pneumococcus, independent of the immune mechanism residing in the blood. This action is the same as that noted *in vitro* when comparable concentrations of drug are added to human blood or artificial media. So far as could be determined, the antibody response in their drug-treated patients was comparable in every respect to that resulting from spontaneous recovery. They seldom found antibodies before the sixth day and agglutinins rarely appeared before the seventh day of the disease.

Sulfapyridine versus Serum. On the whole, sulfapyridine therapy is more efficacious than serum therapy in pneumonia. Unlike antiserum, the drug is definitely effective in Type III pneumococcal pneumonia. It is also useful in cases of mixed infections or pneumonias due to organisms other than the pneumococcus. If the patient is not treated until late in the course of the pneumonia, serum therapy is not effective as a rule; in contrast, sulfapyridine may often give good results. The reason for this may reside in the fact that the anti-pneumococcus action of sulfapyridine is not adversely affected by the soluble specific polysaccharide produced by the capsule of the pneumococcus. This substance is capable, even in high dilution, of combining with the pneumococcus antibody of homologous type to render it ineffective. Sulfapyridine has the further advantage over serum of being cheaper and more generally available. It can be employed in cases where serum therapy is inapplicable, as when the pneumococcus cannot be established as the etiological agent or, if present, is non-typable. Sulfapyridine can be administered by mouth, a definite asset. Whereas serum therapy results in sensitization of the patient which may make repetition dangerous, sulfapyridine can be repeated without harm except when contraindications exist.

Sulfapyridine Combined with Serum. Although sulfapyridine alone is usually quite effective in the therapy of pneumonia, certain conditions exist in which the use of serum along with chemotherapy is indicated. Lord and associates (1940) suggest that chemotherapy and serotherapy be combined under the following conditions: (1) in patients who are fifty years of age or over; (2) in patients in whom treatment is begun after the third day of the disease; (3) when pneumococcus bacteriemia is known to be present; (4) when involvement of more than one lobe is present; (5) in patients who are pregnant or in the first week of the puerperium; (6) if there is no obvious improvement within 18 to 24 hours after inauguration of sulfapyridine treatment, but this interval may be prolonged to 24 to 36 hours in the absence of the aforementioned conditions (1) to (5). When both serum and sulfapyridine are used together, the latter need not be continued for more than one or two days, and the amount of serum needed may be smaller than usual. An authoritative review of the relative merits of sulfapyridine and serum in the therapy of pneumonia may be found in the monograph by Lord, Robinson and Heffron (1940).

Before starting sulfapyridine therapy, sputum should be obtained for typing and a sample of blood taken for culture. The necessity of typing all cases of pneumonia obviously is not altered by the advent of sulfapyridine, and typing is essential for statistical purposes and to establish a bacteriological diagnosis in case serum therapy is needed later.

Pneumococcal Meningitis. Sulfapyridine has been successfully employed in the treatment of pneumococcal meningitis, a disease which was practically always fatal before the advent of chemotherapy. (*See* Reid and Dyke, 1938; Robertson, 1938; MacKeith and Oppenheimer, 1939; Cutts and coworkers, 1939; Barnett and associates, 1939; Toomey and Roach, 1939; Terry and Beard, 1940; MacKay and Hurteau, 1940; and others.) Toomey and Roach reported recovery in six cases of pneumococcal meningitis treated with sulfapyridine, and MacKay and Roach described four cases of the disease successfully treated with the drug. Long and Bliss (1939), however, employed sulfapyridine in six patients ill with the disease. In three, chemotherapy alone was employed and in three the drug was combined with type specific antipneumococcal serum. Only one patient survived. In a series sufficiently large to be of significance, on the other hand, Hodes, Gimbel and Burnett (1939) reported that eight of 17 patients recovered due to sulfapyridine therapy. Four of the fatal cases died within 24 hours after admission to the hospital, and if these are excluded the case mortality is 38 per cent. This compares with a mortality of 100 per cent in 14 patients treated by them before the advent of the sulfonamide drugs (without antipneumococcic serum), and 92 per cent in 12 patients treated with sulfanilamide. Intravenous administration of sodium sulfapyradine (five per cent solution) was employed to supplement oral sulfapyridine therapy and the attempt was made to keep the spinal fluid concentration of free sulfapyridine at a level of from 10 to 15 mgm per cent. Full doses were continued by mouth until the patient was entirely well clinically and until several successive cultures of the spinal fluid were sterile. The dosage was then gradually reduced. Lumbar puncture was performed only for diagnostic purposes and to relieve pressure symptoms.

Pneumococcal Peritonitis. This infection has responded very satisfactorily to sulfapyridine, and nephrotic children have been cured of pneumococcal peritonitis. Barnett and coworkers (1939), for example, record three cases of recovery after sulfapyridine therapy.

Staphylococcal Infections. Although sulfapyridine is more effective than sulfanilamide in staphylococcal infections, it is far from being the powerful chemotherapeutic agent that it is against pneumococcal infections.

Blake and Haviland (1939), for example, obtained no evidence from the use of sulfapyridine in six cases of staphylococcic pneumonia that the drug was of significant value, and Barnett and associates (1939) also had no success with the drug in staphylococcal infections. Several reports, however, have appeared in which sulfapyridine seemingly produced recovery in isolated instances of staphylococcal septicemia (Fenton and Hodgkiss, 1938; O'Brien and McCarthy, 1938; Galewski and Stannus, 1939; Blumenthal, 1940; and others). Abramson and Flacks (1939) recorded two cases of carbuncle of the face with staphylococcal septicemia that recovered after early therapy with large doses of sulfapyridine combined with ligature of the angular vein, whereas four additional patients in whom this treatment was not instituted but who received other sulfonamide drugs succumbed to the infection. Goldberg and Sachs (1939) reported the recovery of two patients with *Staphylococcal aureus* bacteriemia in whom sulfanilamide was ineffective but sulfapyridine rapidly sterilized the blood stream. Long and Bliss (1939) state that the drug proved effective in the treatment of a few cases of staphylococcal pneumonia, and Long (1939) commented on the rapid sterilization of the blood produced in three of five patients ill with staphylococcic bacteremias.

Obviously the status of sulfapyridine in staphylococcal infections cannot yet be stated. When employed, the drug should be given in doses designed to yield a blood level of the free fraction of 10 mgm per cent or more. Other derivatives such as sulfathiazole in time may be shown to be more effective than sulfapyridine against staphylococci.

Friedländer's Bacillary Infections. The marked efficacy of sulfapyridine in the treatment of Friedländer's bacillus infections in mice fostered the hope that the drug would be highly useful in the treatment of human infections due to this organism. Clinical data on the employment of sulfapyridine are meager. Meyer and Amtman (1939) reported recovery following use of the drug in a patient with septicemia due to Friedländer's bacillus (portal of entry unknown). Long and Bliss (1939) administered sulfapyridine in a case of Friedländer's bacillary pneumonia, and although a heavy bacteremia was reduced practically to nil the patient succumbed. Obviously much more experience is required, but it appears that sulfapyridine is one of the few effective sulfonamide drugs available against this organism.

Meningococcal Infections. Sulfapyridine has been successfully employed in meningococcal infections including *meningitis* and *meningococcemia.* Dimson

(1938), for example, recorded the cure of a patient with meningococcemia. Hobson and MacQuadie (1938) reported recovery in their six cases of meningococcal meningitis. Banks (1939) noted few complications and only one death in a group of 36 patients treated with sulfapyridine, and later (1940) states that the drug is the sulfonamide derivative of choice in the therapy of cerebrospinal fever. Jordan and associates (1940) reported that the mortality rate in 50 cases of meningococcal meningitis given sulfapyridine was 32 per cent, as compared to 38 per cent in 50 cases treated with antimeningococcal serum, 26.6 per cent in 30 cases given both sulfapyridine and serum, and 20 per cent in 30 cases given sulfapyridine in combination with meningococcal antitoxin. Sulfapyridine-treated patients had a more favorable clinical course, the headache and rigidity disappearing rapidly, recovery occurring more quickly, and relapses being noted only rarely. Although it is thus apparent that sulfapyridine is effective against meningococci, it is not definitely known whether the drug is of greater clinical value than sulfanilamide. Since sulfapyridine is the more toxic agent, preference probably should be given to sulfanilamide.

Gonococcal Infections. Sulfapyridine has been employed sucessfully in the treatment of gonococcal infections including *gonorrhea, ophthalmitis, vulvovaginitis,* and *endocarditis.* Gonorrhea in both men and women has yielded satisfactorily to sulfapyridine medication (Lloyd and coworkers, 1938; Durel, 1938; McGregor-Robertson, 1939; Batchelor and associates, 1938, 1940; Cook and Sutton, 1939; Johnson and associates, 1939; and others). For example, the review of Thomas cites 1450 cases in which sulfapyridine was used and 85 per cent were recorded as cures. The doses employed by different investigators vary; but they average approximately three grams a day in four divided portions for four or five days, and then reduced amounts (1.5 to 2.0 grams daily) are given for one or two weeks. The status of sulfapyridine therapy in gonorrhea cannot yet be stated or an exact comparison made between sulfapyridine and sulfanilamide. However, a number of competent observers believe that sulfapyridine is more effective than sulfanilamide. (*See* Thomas, 1939; Van Slyke and coworkers, 1939; Herrold, 1939; Batchelor and associates, 1940; Pelouze, 1940. There is good evidence that sulfapyridine is more toxic than sulfanilamide and it perhaps may be more dangerous to employ in ambulatory patients (Cokkinis and McElligott, 1938). Furthermore, acetylsulfapyridine may result in irritation to the urinary tract. In addition, the percentage of very late relapses, as distinct from chemotherapeutic failures and early relapses, has been shown by Cokkinis and McElligott (1939), from an analysis of 1268 cases of gonorrhea in the male, to be much higher after sulfapyridine therapy (18.5 per cent) than following treatment with sulfanilamide (7.8 per cent). Long and Bliss (1939) succinctly present the problem when they state, "It is perhaps unfortunate that this drug has popped out of the box into the arena of controversy, before the merits of sulfanilamide and the sulfanilyl sulfanilamides in the therapy of gonorrhea have been established, because it adds another unknown to an already difficult equation." Nevertheless, the opinion is growing firmer that sulfapyridine is definitely superior to sulfanilamide and should be preferred to it in the treatment of gonococcal infections.

Streptococcal Infections. Although more information is needed, it appears that sulfapyridine will probably prove about as effective as sulfanilamide in the therapy of *beta* hemolytic streptococcal infections in man, and reports as to its value in erysipelas, scarlet fever, acute tonsillitis, pneumonia and meningitis have already been published. However, due to its greater toxicity and the lack of demonstrable superiority over sulfanilamide, sulfapyridine should not be the drug of choice in streptococcal infections (Long and Bliss, 1939; Blake and Haviland, 1939).

Few data exist as to the value of sulfapyridine in infections due to the *alpha* hemolytic streptococcus. Whitby (1938), Ellis (1938) and Jones (1939) each reported temporary improvement in patients with subacute bacterial endocarditis due to *Streptococcus viridans.* Long and Bliss (1939) noted temporary benefit from sulfapyridine therapy in one of their two patients with the same disease, and Barnett and associates (1939) reported a similar case. The combined use of sulfonamide drugs and heparin may possibly provide a new therapeutic attack on bacterial endocarditis and the preliminary reports of Kelson and White (1939) and Friedman and coworkers (1939) indicate that sulfapyridine used in conjunction with heparin has produced striking improvement in a limited number of patients with the disease. The future results of this new treatment obviously will be followed with interest. The rationale for the use of heparin is discussed on page 1145. The successful employment of sulfapyridine in the treatment of patients with meningitis due to *Streptococcus viridans* has been reported by Mitchell and associates (1940).

Miscellaneous Infections. Sulfapyridine has been employed in a large number of infections with varying success, but the data are insufficient to allow critical appraisal of the value of the drug in any of these. In *lymphopathia venereum,* sulfapyridine has been employed with promising results (Ross, 1939; Earle, 1939; and others). In five patients with *influenzal meningitis,* Waring (1939) reported recovery in two and temporary benefit in two of the three who died, as contrasted with no recoveries in six patients given sulfanilamide and nine receiving no specific treatment. Sakula (1940) also reported recovery in a case of meningitis due to *Pfeiffer's bacillus* and treated with sulfapyridine. Barnett and coworkers (1939), however, obtained no benefit from sulfapyridine in two patients with influenzal meningitis. In *pulmonary tuberculosis,* Allison and Myers (1939) could detect no improvement from sulfapyridine therapy in seven active cases, one with generalized miliary tuberculosis, and Barnett and associates (1939) observed no benefit from the drug in a patient with *tuberculous meningitis.*

SULFATHIAZOLE

Sulfathiazole and sulfamethylthiazole were synthesized in 1939 independently by Fosbinder and Walter, and Lott and Bergeim. They are sulfanilamide derivatives of heterocyclic amines and represent the thiazole analogues of sulfapyridine. The structural formula of sulfathiazole is given in Table 52. Sulfamethylthiazole differs only in having a methyl group attached to the carbon in position 4 in the thiazole nucleus.

Information concerning the ultimate chemotherapeutic value and toxic potentialities of these compounds is incomplete and one must therefore await the accumulation of a sufficient number of authoritative reports concerning their pharmacology, toxicology and therapeutic indications. The publication of a preliminary report (Long, 1940) was authorized by the Council on Pharmacy and Chemistry. Sulfathiazole was released for distribution and general clinical use by the Federal Food and Drug Administration in August, 1940. Sulfamethylthiazole has not been made available and appears to be more toxic than sulfathiazole, causing a high incidence of peripheral neuritis.

Action In Vitro Against Bacteria. The sulfathiazoles have shown promising antibacterial actions when tested *in vitro* against a variety of microörganisms. Sulfathiazole is as bacteriostatic as sulfapyridine when tested in broth cultures against certain strains of Lancefield's Groups A, D, and G *beta* hemolytic streptococci, *B. coli, Staphylcoccus aureus*, Types I and II pneumococci, and *B. proteus* (Long and Bliss, 1940). Sulfathiazole was found by King and Henschel (1940) to be as effective as sulfanilamide in exerting a bacteriostatic action against *beta* streptococci grown by the Maximow culture technic. Sulfamethylthiazole was somewhat less effective. In broth cultures containing concentrations as low as five mgm per cent, sulfathiazole, sulfamethylthiazole, and sulfaphenylthiazole were shown by Lawrence (1940) to be superior to sulfanilamide and sulfapyridine in their inhibitory action on the growth of pneumococci Types I, II and III, and Group A *Streptococcus hemolyticus*. When concentrations of one mgm per cent were used, the thiazole derivatives also proved to be more effective than sulfanilamide and sulfapyridine against the gonococcus. The methyl and phenyl compounds exhibited marked bacteriostatic effects on *Staphylococcus aureus*, whereas sulfanilamide and sulfapyridine showed only a moderate degree of inhibition of growth of this organism.

Rammelkamp and Keefer (1940) have also demonstrated the bacteriostatic and bactericidal action of the sulfathiazoles against staphylococci. Concentrations of sulfathiazole of 2.5 to 5.0 mgm per cent were optimally effective in inhibiting *Staphylococcus aureus* in defibrinated whole blood. Sulfamethylthiazole was slightly less active. Sulfanilamide was almost impotent against the staphylococcus and sulfapyridine exhibited only limited value. Blood taken from human beings receiving sulfathiazole orally showed an increase in bacteriostatic and bactericidal power against staphylococci. Rake and McKee (1940), while noting the bacteriostatic action of the sulfathiazoles against *Staphylococcus aureus*, found sulfamethylthiazole to be more potent than sulfathiazole. However, both compounds were more effective than sulfapyridine. Herrell and Brown (1939) have also reported sulfamethylthiazole to be more active *in vitro* than sulfathiazole and sulfapyridine against *Staphylococcus aureus*. Bayliss (1940) demonstrated that sulfathiazole, as well as sulfanilamide and sulfapyridine, did not inactivate various staphylococcal toxins *in vitro*.

Sulfathiazole and particularly sulfamethylthiazole have been shown to possess a marked antibacterial effect on microörganisms occurring in the human urinary tract (Helmholz, 1940). For example, *Streptococcus faecalis*, an organism unaffected by sulfanilamide or sulfapyridine, and various strains of *Proteus ammoniae* were readily killed by the thiazole compounds. Sulfathiazole but not sulfamethylthiazole was found by Helmholz rapidly to kill six different strains of *Pseudomonas aeruginosa*. These experiments were performed by inoculating urine, obtained from patients receiving the drugs, with the various bacteria tested. Hill (1940) could not distinguish any striking differences in the *in vitro* bactericidal power in human urine of sulfathiazole, sulfanilamide and sulfapyridine. However, urines passed by patients receiving sulfathiazole were noted by her to exert much more germicidal action than urine to which had been added an equivalent concentration of the drug. The bacteria tested were *Staphylococcus aureus, alpha Streptococcus faecalis, Aerobacter,* and *Proteus.*

Sulfathiazole was demonstrated by Lawrence (1940) to be the most active of the sulfonamide drugs tested in exerting bacteriostatic effects *in vitro* on bacteria representative of the colon-typhoid-dysentery group, followed in decreasing order of potency by sulfamethylthiazole, sulfapyridine, sulfaphenylthiazole, and sulfanilamide. Both hemolytic and nonhemolytic *enterococci* were found to be inhibited in their growth by sulfathiazole and sulfamethylthiazole (Neter, 1940). A similar concentration of sulfanilamide was not bacteriostatic under the same conditions and sulfapyridine only delayed growth.

Action In Vivo Against Experimental Infections. *Pneumococcal Infections.* Preliminary investigations by McKee and her coworkers (1939) indicated that sulfathiazole (given as one per cent of the diet) is equal in effectiveness to sulfapyridine against experimental infections in mice produced by various types of pneumococci. Barlow and Homburger (1940) likewise demonstrated that sulfathiazole and sulfamethylthiazole, administered orally, protected mice infected with Types I, II, and III pneumococci as efficiently as did sulfapyridine. Sulfaphenylthiazole was somewhat inferior to the other thiazoles. Cooper and associates (1939) found the thiazole derivatives to be slightly less potent than sulfapyridine in pneumococcal (Type II) infections in mice. A similar finding in pneumococcal infections (Type I) in mice was reported for sulfathiazole by Long and Bliss (1940) who pointed out, however, that the administration of the drug in acacia suspension by the oral route invalidated their results to a certain extent, because of the more rapid absorption and excretion of sulfathiazole as compared to sulfapyridine. In a study of sulfonamide therapy of Type I pneumococcus infections in mice, Litchfield, White and Marshall (1940) observed that sulfathiazole was slightly more effective than sulfapyridine and nearly three times as potent as sulfanilamide when the blood concentrations of the drugs were equal. From the aforementioned investigations, therefore, it is clear that sulfathiazole is at least as protective as sulfapyridine when tested in experimental pneumococcal infections in animals.

Staphylococcal Infections. Sulfathiazole has been shown by several investigators to be quite active in protecting animals infected experimentally with staphylococci. Barlow and Homburger (1939) observed that sulfathiazole and sulfamethylthiazole were more effective than sulfapyridine in prolonging the life of mice experimentally infected with a highly mouse-virulent strain of *Staphylococcus aureus,* and the compounds inhibited the development and allowed the healing of abscesses in various organs. Bliss and Ott (1940) confirmed these observations. Sulfathiazole was found by Rake and McKee (1940) to be slightly but consistently more potent than sulfamethylthiazole against staphylococcal infections in mice. Sulfapyridine, in their experiments, had little if any protective value. The efficacy of sulfamethylthiazole in staphylococcal infections in mice has also been reported by Carroll and associates (1940), Herrell and Brown (1939), and Jones and associates (1940). From the aforementioned experiments, it can be stated that the sulfathiazole compounds are more protective than sulfanilamide or sulfapyridine in staphylococcal infections in experimental animals.

Streptococcal Infections. Sulfathiazole and sulfamethylthiazole were observed by Cooper and coworkers (1939) to be approximately as potent as sulfanilamide and slightly less active than sulfapyridine in experimental streptococcal infections in mice. However, Barlow and Homburger (1940) found the efficacy of thiazole derivatives in experimental *beta* hemolytic streptococcal infections in mice to be from two to three times that of sulfanilamide and approximately equal to that of sulfapyridine. McKee and associates (1939) fed sulfathiazole in one per cent concentration in the diet and found the drug to exert the same order of chemotherapeutic action as sulfapyridine in mice infected with *Streptococcus hemolyticus.*

Miscellaneous Infections. Sulfathiazole appears to exert an action equal to that of sulfapyridine when given to mice infected with *meningococci* Type II, according to the experiments of McKee and coworkers (1939). These investigators also found that sulfathiazole protected mice against *lymphogranuloma venereum* infection but not against the virus of *herpes simplex* or *swine influenza.* Sokhey and Dikshit (1940) reported that sulfathiazole given orally cured 80 per cent or more of mice infected with *plague,* proving superior to sulfapyridine and equal to an effective antiplague serum.

Margin of Safety. The *acute toxicity* of the thiazole derivatives of sulfanilamide has been tested in several laboratory animals by a number of investigators. VanDyke and associates (1939) found that sodium sulfathiazole administered parenterally is less acutely toxic than sodium sulfapyridine in mice, rats, and monkeys. This observation has been confirmed by Long, Haviland and Edwards (1940) who noted that the acute toxicity of sulfathiazole for mice (as measured by the parenteral injection of sodium salts) was approximately one-half that of sulfapyridine, sulfamethylthiazole or sulfaphenylthiazole, but it was one-third greater than that of sulfanilamide. Thus the sodium salts of the methyl and phenyl derivatives were approximately as acutely toxic for mice as sodium sulfapyridine whereas sodium sulfathiazole was definitely less toxic. Barlow and Homburger (1940), however, reported that sodium sulfapyridine administered orally to mice is 1.4 times more toxic than sodium sulfaphenylthiazole, 3.4 times more toxic than sodium sulfamethylthiazole, and 4.6 times more toxic than sodium sulfathiazole.

The *chronic toxicity* of the thiazole derivatives has also been investigated. VanDyke and associates (1939) found the chronic toxicity of sulfathiazole in mice to be greater than that of sulfapyridine when the two drugs were fed as two per cent of the diet. However, when the compounds were given in amounts comparable to those employed clinically, sulfathiazole was no more toxic than sulfapyridine. In monkeys and growing rats, sulfapyridine was clearly the more toxic drug, the principal damage from sulfapyridine being to the kidney and urinary tract. Rake and coworkers (1940) observed microscopic lesions in the kidney, liver, and spleen of mice chronically poisoned with sulfathiazole. In rats and monkeys, little evidence of injury was noted, even following intensive therapy with sulfathiazole. Barlow and Homburger (1940) also observed that the three thiazole derivatives were less toxic than sulfapyridine upon daily oral administration of large doses to mice over a ten-day period.

Gross and coworkers (1940) gave large doses (0.5 gram per kg orally once or twice daily) of sulfathiazole and sulfamethylthiazole to rats for periods up to 11 days and noted urolithiasis associated with secondary infection and pyelonephritis which occasionally caused death. The uroliths were composed of both free and conjugated forms of the drugs. The involvement of the urinary tract by the sulfathiazoles was found to be less common than after similar administration of sulfapyridine. However, sulfathiazole uroliths were observed more frequently in the renal tubules whereas sulfapyridine uroliths were usually precipitated in the extra-renal urinary passages.

Obviously, the species being studied determines to a considerable extent the toxicity of the thiazole derivatives, and it appears in most experiments that sulfathiazole, at least, has a greater margin of safety than sulfapyridine.

Absorption, Distribution, Fate and Excretion. At present, sulfathiazole appears to be the most promising of the thiazole derivatives of sulfanilamide from a clinical point of view. Inasmuch as more information is available concerning sulfathiazole than its methyl or phenyl congeners, the following description pertains chiefly to sulfathiazole.

Absorption. Sulfathiazole is *rapidly and adequately absorbed* from the intestinal tract. Both experimental and clinical observations indicate that it approaches sulfanilamide in this respect and differs sharply from sulfapyridine (Long and coworkers, 1940; Sadusk, Blake and Seymour, 1940; Reinhold and associates, 1940). In man, a single oral dose of sulfathiazole of 0.06 gram per kg allows a peak concentration of the drug in the blood within two to three hours after ingestion. The blood level obtained by this dose varies from 1.5 to 8.0 mgm per cent (total sulfathiazole) but in most cases averages approximately 3.0 to 6.0 mgm per cent (Sadusk and coworkers, 1940). The blood level falls sharply if medication is not continued, and decreases considerably by the sixth hour after ingestion of a single large dose. When sodium sulfathiazole is given orally, its absorption is so rapid that the curve of its concentration in the blood resembles that obtained following the intravenous injection of its sodium salt. Absorption of sodium sulfathiazole by the *rectum* is slow and quite incomplete (Reinhold and coworkers, 1940). Fortunately, the oral administration of sulfathiazole is so satisfactory and causes vomiting so infrequently that the rectal route is rarely if ever indicated.

When a single initial oral dose of three to four grams of sulfathiazole is given and followed by doses of one gram at four-hour intervals, the blood concentration of total sulfathiazole averages, as a rule, between 4.5 and 6.5 mgm per cent (Sadusk and coworkers, 1940; Reinhold and collaborators, 1940). However, marked variations may be noted in individual cases. The range of blood concentrations with continued sulfathiazole therapy appears, in the main, to be quite similar to that noted with sulfapyridine, the median value tending to be somewhat lower than that for total sulfapyridine.

Distribution. The distribution of sulfathiazole in the various compartments of the body fluids appears to be similar to that of sulfanilamide and sulfapyridine. The drug readily enters the *pleural* and *peritoneal* fluids as well as *exudates,* and it reaches a concentration in these loci approximately as high as that attained in the blood. Conjugated sulfathiazole diffuses more slowly than the free form. For some reason as yet not understood, sulfathiazole apparently does not readily penetrate into the *cerebrospinal fluid* (Sadusk and associates, 1940). Even when peak blood concentrations are present after two days of sulfathiazole therapy, no drug or only a negligible trace is detectable in the normal spinal fluid. The latter usually contains less than one mgm per cent of total sulfathiazole at a time when the blood concentration is six to eight mgm per cent. This fact would appear to be a handicap in the therapeutic use of the compound by mouth or parenterally in patients with meningitis, and stands in sharp contrast with the ready diffusibility of sulfanilamide and sulfapyridine into the cerebrospinal fluid.

Fate. Sulfathiazole is conjugated in the body by acetylation. The degree of acetylation approaches that for sulfanilamide and is considerably below that for sulfapyridine. Sadusk and coworkers (1940) found in a large series of patients (79) that the extent of acetylation, with a few exceptions, varied from zero to 30 per cent, the median being approximately 12 per cent. The low percentage of conjugated sulfathiazole is a distinct advantage of the compound over sulfapyridine, the degree of acetylation of which is highly capricious and unpredictable and varies over a wide range (15 to 75 per cent or more). The fact that nearly all the sulfathiazole in the blood is present in the therapeutically active free form makes the maintenance of effective blood levels of the drug relatively easier.

Acetylsulfathiazole diffuses slowly into pleural and ascitic fluid and is absent (or present only in traces) in the normal spinal fluid. If sulfathiazole medication is continued in patients in whom renal function is impaired, the blood concentration of total sulfathiazole rises to high levels and the degree of acetylation is abnormally excessive (30 to 65 per cent). This phenomenon is also true of sulfapyridine and sulfanilamide, and enjoins caution in the administration of sulfonamide drugs to patients with cardiac or renal failure.

Excretion. Excretion of sulfathiazole by the kidneys is rapid if renal function is adequate. The drug is eliminated more quickly than sylfapyridine, 40 per cent of a single orally ingested dose being excreted in the urine within six hours and 70 to 80 per cent by the end of 24 hours, at which time only traces remain in the blood (Sadusk and associates, 1940). Excretion values ranging from 84 to 93 per cent in 24 hours were obtained after oral administration by Reinhold and coworkers (1940), and sodium sulfathiazole injected intravenously was recovered to the extent of 97 per cent. These investigators also observed that in the presence of impaired renal function, clearances of both free and conjugated sulfathiazole were lowered, the conjugated to a greater extent than the free form. It is thus clear that sulfathiazole is eliminated by the kidney at a rate similar to that for sulfanilamide, and more rapidly and completely than sulfapyridine. In large part, this rapidity and completeness of renal excretion is a reflection of the rapid and complete intestinal absorption of the drug.

Sulfathiazole is eliminated by the kidney in the free and acetylated forms, and crystals of both of these compounds can be identified in the urine. The percentage of the total amount of sulfathiazole present in the urine as acetylsulfathiazole varies considerably (five to 45 per cent) but ranges as a rule between 10 and 30 per cent. These values are considerably lower than those for sulfapyridine and sulfanilamide. Inasmuch as acetylsulfathiazole is quite insoluble (being three times less soluble in water than acetylsulfanilamide) and thus may precipitate out in the renal tubules and urinary tract, the lower degree of acetylation of sulfathiazole is a distinct advantage of the compound over sulfapyridine.

Information concerning channels of excretion of sulfathiazole other than the kidneys is meager, but there is little reason to doubt that it is eliminated in small amounts by the same routes as described for sulfanilamide.

Effective Blood Levels. Within a few hours after administration of sulfathiazole, effective blood levels are reached. For example, when the usual initial dose of four grams is taken orally, peak blood levels are attained in approximately two to three hours. If additional sulfathiazole is not administered, the blood concentration does not begin to fall appreciably until the fifth or sixth hour. A four gram dose usually yields a blood level of free sulfathiazole of from 3.0 to 6.0 mgm per cent, the level of total sulfathiazole being very little higher—approximately 3.5 to 7.0 mgm per cent. In severe infections, such as pneumococcal pneumonias, a blood concentration of free sulfathiazole of from 3.0 to 5.0 mgm per cent has been found to give satisfactory therapeutic results.

The concentration of sulfathiazole in the pleural and ascitic fluids is approximately 75 per cent of that of the blood within four hours and is the same as that of the blood after 24 hours. The low concentration of sulfathiazole in the spinal fluid has already been mentioned.

Preparations. *Sulfathiazole* is a white, crystalline powder which is poorly soluble in water. At 28 C., only 90 mgm dissolve in 100 cc of water (0.09 per cent concentration). The saturated aqueous solution has a pH of 6.0. *Sodium sulfathiazole,* in contrast, is soluble in water to the extent of approximately five per cent, the solution being highly alkaline (pH 10.5). Sulfathiazole and its sodium salt are not official drugs and are not as yet described in N.N.R. However, the Council (1940) has adopted "sulfathiazole" as a nonproprietary name. Sulfathiazole is supplied for oral use in 0.5 gram tablets. Sodium sulfathiazole may be obtained in powder form for preparation of solutions for parenteral administration.

Doses and Route of Administration. Sulfathiazole is usually administered *by mouth.* This is practical because the rapid intestinal absorption of the drug permits effective blood concentrations to be reached without delay, and because of the absence of severe nausea and vomiting. In both of these important respects, sulfathiazole differs from and has an advantage over sulfapyridine. If parenteral administration is necessary, *sodium sulfathiazole* may be given *intravenously* by the same technic as for sodium sulfapyridine. A 5.0 per cent sterile aqueous solution is employed and the injection is made very slowly, the same precautions being observed as outlined previously for sodium sulfapyridine.

The *dose* of sulfathiazole for patients ill with severe infections is similar to that for sulfapyridine, an initial 4.0 gram dose being given orally in adults and followed by 1.0 gram doses at four-hour intervals day and night. This scheme usually results in satisfactory blood levels of the drug. The concentrations of free and total sulfathiazole in the body fluids may be determined by the method of Marshall and associates as outlined previously for sulfanilamide. For routine purposes, it is adequate to determine only the level of free sulfathiazole because the amount of acetylated drug usually found in the blood is small.

Clinical Toxicity. All the possible toxic manifestations of sulfathiazole medication are not as yet known, but the evidence available suggests that, although the drug is less toxic than sulfapyridine, it is capable of producing most of the untoward reactions seen after administration of sulfapyridine and sulfanilamide. The incidence, time of appearance, severity, and clinical significance of the toxic actions of sulfathiazole as compared to those of sulfanilamide and sulfapyridine are indicated in Table 55, compiled by Long and associates (1940) from their experiences with sulfathiazole in 271 hospitalized adults.

Nausea and Vomiting. These are uncommon after sulfathiazole. Serious vomiting is quite rare, sharply contrasting with the severe emesis occurring after sulfapyridine. In a series of 120 patients receiving sulfathiazole for pneumococcal pneumonia, Blake and Sadusk (1940) did not observe a single instance in which oral therapy had to be discontinued because of vomiting. Similar results were reported by Reinhold and coworkers (1940) who noted nausea or vomiting in only seven of 87 patients given sulfathiazole. Emesis was mild, did not require cessation of oral medication, and nausea was absent between attacks. In 100 cases reported by Flippin and associates (1940), nausea occurred in 25 per cent and vomiting in 13 per cent. However, severe emesis was not observed. Similarly, Finland and coworkers (1940) recorded nausea and vomiting in 45 per cent of 165 patients, but the incidence and severity were less than with sulfapyridine medication. Spink and Hansen (1940) noted nausea and vomiting in only six of 100 patients treated with sulfathiazole.

Central Nervous System Phenomena. These are uncommon after sulfathiazole. *Dizziness* is unusual. *Psychosis* occurred in one of the 120 cases of Blake and Sadusk. Four questionable instances were reported in 100 patients by Flippin and associates, and these investigators point out the difficulty of ascribing psychosis to sulfathiazole in patients with an acutely febrile disease like pneumonia. However, Finland and coworkers (1940) observed psychoses in three patients (in a series of 165) in whom fever had subsided, and Abernethy recorded four patients (in a series of 35) in whom delirium developed. *Peripheral neuritis* from sulfathiazole is extremely rare, although Blake and Sadusk observed an unquestionable case of bilateral protracted ulnar neuritis in a patient who developed an excessively high blood level of sulfathiazole. Peripheral neuritis is the major serious toxic effect of sulfamethylthiazole.

Dermatitis. Cutaneous eruptions are somewhat more common after sulfathiazole than after sulfanilamide or sulfapyridine. Long and associates observed an incidence of five per cent (Table 55), a figure the same as that found by Blake and Sadusk, and approximating that noted by Flippin and coworkers (four per cent) and by Finland and associates (slightly under five per cent). Spink and Hansen (1940), however, observed dermatitis in nine per cent of 100 patients receiving sulfathiazole. The time of appearance and significance of the skin rashes are the same as described in detail for sulfanilamide. The cutaneous eruptions may be nodular in character and may resemble erythema nodosum.

Injection of the Sclera and Conjunctiva. This reaction has not been reported due to sulfanilamide or sulfapyridine, but it may occur after sulfathiazole. It may develop along with the skin rash which is then usually an erythematous papular or nodular eruption generalized over the extremities and face. Congestion of the conjunctiva was observed in four per cent of the cases reported by Long and associates and has also been noted by Blake and Sadusk and by Flippin and coworkers in isolated instances. The condition resembles "pink eye" and generally occurs between the fifth and ninth day. Its appearance is frequently heralded by burning and smarting of the eyes, and a watery discharge. In some cases, an element of heliosensitivity appears to exert an etiological rôle (Haviland and Long, 1940).

Cyanosis and Acid-Base Balance Disturbance. Cyanosis apparently is uncommon after sulfathiazole. It was not observed in the series of Blake and Sadusk or by Reinhold and associates. Disturbances of the *acid-base balance* have not been reported to occur due to sulfathiazole medication and sodium bicarbonate need not be given with it. Likewise *jaundice* is rarely noted, having been recorded in only two cases in the series of 165 patients observed by Finland and coworkers.

Drug Fever. Fever is more common after sulfathiazole than after sulfapyridine, and its incidence is approximately the same as that for sulfanilamide, namely, 10 per cent. The fever is usually mild, but it probably has the same significance as outlined for sulfanilamide fever.

Urinary Tract Disturbances. These are similar to those discussed in detail for sulfapyridine. They are due in large part to the precipitation in the renal tubules and extra-renal urinary tract of the insoluble acetylsulfathiazole. Hematuria occurred in 2.5 per cent of the 271 cases of Long and coworkers. Likewise, in only three of the 120 patients of Blake and Sadusk was hematuria noted. It was microscopic in character, and gross hematuria was not encountered. Flippin and coworkers recorded an incidence of microscopic hematuria of six per cent in 100 patients but did not observe a single case of gross hematuria. However, gross hematuria was noted in three instances in the series of 165 patients reviewed by Finland and associates. Microscopic hematuria occurred in three of their cases. The differences in incidence of microscopic hematuria reported by various observers may well depend on whether the urine sample is centrifuged. *Renal colic* may occur after sulfathiazole, but the absolute incidence is very low. Finland and collaborators recorded six cases of nitrogen retention in 165 patients (N.P.N. between 50 and 70 mgm per cent). In their series, sulfathiazole crystals were detected in the urine in 26 patients. Nitrogen retention occurred in only one of 35 patients given sulfathiazole for pneumonia by Abernethy. Isolated cases of gross hematuria or crystalline concretions in the renal tubules following the administration of sulfathiazole have been reported by Knoll and Cooper (1940), Pepper and Horack (1940), and Arnett (1940). The exact incidence of complications of the kidneys and urinary tract following sulfathiazole in comparison with sulfapyridine cannot as yet be stated, but the mechanism, significance, and treatment of this type of untoward reaction are the same as previously outlined. Inasmuch as sulfathiazole tends to precipitate in the renal tubules, rather than in the extrarenal urinary passages as in the case of sulfapyridine, the warning signs of albuminuria, casts and oliguria are more common than gross hematuria and renal colic.

Blood. Acute hemolytic anemia and *agranulocytosis* were not reported in the total of 491 cases in the combined reports of Long and associates, Flippin and coworkers, and Blake and Sadusk. However, this is no guaranty that such toxic reactions may not be caused by the drug, and therefore the blood must be examined carefully each day in all patients receiving sulfathiazole. *Mild leukopenia with granulocytopenia* occurs occasionally but ceases rapidly when medication is withdrawn.

Joints. Exquisitely tender, swollen joints have been observed during therapy with sulfathiazole in a few patients (Long and coworkers, 1940). This toxic reaction may offer a puzzling diagnostic problem when the patient is suffering from gonorrhea because of the resemblance to acute gonococcal arthritis.

Therapeutic Uses

As previously mentioned, all the therapeutic uses of sulfathiazole have not been demarcated and further clinical experience is required before definite statements can be made concerning the ultimate value of the drug in comparison with other sulfonamide derivatives. Preliminary experience would appear to indicate that sulfathiazole may seriously challenge sulfapyridine as the agent of choice in pneumococcal infection. It also appears to be more potent than sulfapyridine in staphylococcal infections.

The *contraindications* and *precautions* to be observed in the therapeutic administration of sulfathiazole are similar to those previously outlined in detail for sulfanilamide and sulfapyridine. The doses and routes of administration likewise have already been described.

Pneumococcal Infections. Sulfathiazole has been shown to possess considerable promise in the therapy of pneumococcal infections, including *pneumococcal pneumonia, bacteriemia* and *empyema.* It is not known whether sulfathiazole will prove efficacious in the therapy of *pneumococcal meningitis,* at least when given by the oral or intravenous route. As already stated, in normal persons the drug penetrates very poorly and slowly into the cerebrospinal fluid. Whether this is likewise true for patients with meningitis is not determined. Three patients with pneumococcic meningitis were treated with sulfathiazole and specific antipneumococcus rabbit serum by Spink and Hansen (1940). One patient survived despite low concentrations of the drug in the spinal fluid. In one of the two patients who succumbed, the concentration in the spinal fluid was 60 per cent that of the blood.

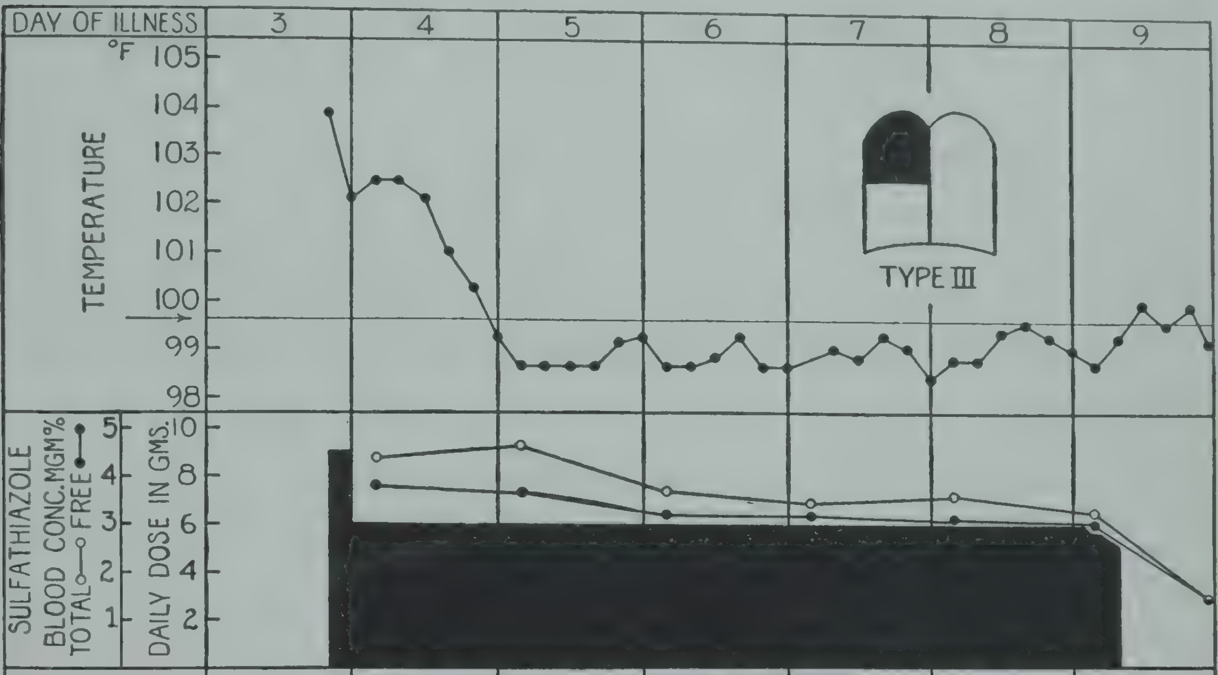
Pneumonia. If the promise of early reports are borne out by further experience, sulfathiazole may supplant sulfapyridine in the treatment of pneumococcal pneumonia. This is true not only because of the high antipneumococcal potency of the drug but also because absorption of sulfathiazole from the intestinal tract is more rapid and complete, the oral route can be used in most patients throughout the course of the disease, nausea and vomiting are mild and infrequent, the sulfathiazole in the blood is nearly all in the therapeutically active free form, and less of the urinary sulfathiazole is conjugated.

In 120 patients with pneumococcal pneumonia treated with sulfathiazole by Blake and Sadusk (1940), the gross mortality was 4.2 per cent and the corrected mortality only 0.8 per cent. These results are equal to or better than those previously obtained with sulfapyridine by these investigators. In no case in which bacteriemia was present did sulfathiazole alone fail to sterilize the blood stream. Oral medication was adequate and in no instance did sulfathiazole have to be withdrawn because of untoward responses. Satisfactory blood levels of sulfathiazole appeared to be between 3.0 and 5.0 mgm per cent of the free form. One of their most striking cases was that of the rapid recovery of a patient with Type III pneumococcal pneumonia involving two lobes and complicated by bacteriemia, leukopenia, cirrhosis of the liver, and chronic alcoholism. The dramatic clinical course of this patient is depicted in Figure 102.

In a series of 100 patients with pneumococcal pneumonia treated with sulfathiazole and carefully compared with a second series of 100 cases of the disease receiving sulfapyridine, Flippin and coworkers (1940) found the two drugs to be equally effective. Finland and associates (1940) employed sulfathiazole in 104 patients with pneumococcal pneumonia, the mortality rate being 11.5 per cent, a figure comparing favorably with those from previous series of patients treated by these investigators with sulfapyridine. In some cases, satisfactory clinical responses were noted with blood levels of free sulfathiazole as low as 1.0 to 2.0 mgm per cent. Occasionally, a five per cent solution of the sodium salt was employed intravenously, or it was injected subcutaneously (five grams in one liter of five per cent glucose solution). Abernethy (1940) used sulfathiazole in 35 cases of pneumonia and reported a mortality rate of 11.4 per cent. In his 31 cases of proved pneumococcal pneumonia, the mortality rate was 6.4 per cent. This investigator was also of the opinion that sulfathiazole compares favorably with sulfapyridine in the chemotherapy of pneumococcal pneumonia. Spink and Hansen (1940) used sulfathiazole in 33 patients with lobar and atypical pneumococcal pneumonia and only one death occurred.

As far as is known at present, the indications for the use of serotherapy in conjunction with sulfathiazole, the question of the optimal duration of treatment, and the effects of the drug on the development of the immune processes in pneumococcal pneumonia are controlled by the same factors previously outlined in detail for sulfapyridine.

Staphylococcal Infections. A rapidly growing number of clinical reports testify to the value of sulfathiazole in a large variety of staphylococcal infections. These include *furunculosis, septicemia, contaminated wounds* and *fractures, osteomyelitis, cellulitis, cortical abscesses of the kidney, sinusitis, otitis media, mastoiditis, epidural abscess,* etc. References to the use of sulfathiazole in the aforementioned staphylococcal infections are as follows: Carroll and coworkers (1940); Fitch (1940); Grulee and Mason (1940); Herrell and Brown (1939); Keliher and Carlen (1940); Key and Frankel (1940); Levin (1940); Stirling (1940); Spink and Hansen (1940). Spink and Hansen reported recovery in all 15 of their cases of staphylococcal septicemia.



PERCENTAGE ACETYLATION			12%		20%	16%	6%	14%	9%
BLOOD CULTURE		+	−						
W.B.C. TOTAL	4,100		2,650	6,400	5,600	8,900	8,200	11,500	11,100
NON-SEG.	10%		8%	20%	8%				
SEGMENTED	54%		44%	50%	64%				

FIGURE 102. *Clinical efficacy of sulfathiazole in pneumococcal pneumonia.*

White male, aged 47; chronic alcoholism; portal cirrhosis, with the liver edge eight centimeters below the costal margin and impaired hepatic function as measured by the bromsulfalein excretion test; arteriosclerotic heart disease; type III pneumococcal lobar pneumonia involving right upper lobe, questionable involvement of the right middle lobe. The patient was admitted to the hospital on the third day of the pneumonia, critically ill and suffering from a toxic psychosis. Sulfathiazole therapy by mouth was immediately instituted, four grams being given initially and one gram every four hours thereafter. The blood levels of free and total sulfathiazole and the percentage acetylation resulting from this scheme of medication are indicated in the chart. Nausea and vomiting did not occur. Note the sharp decline in the patient's temperature (all readings indicate rectal temperature) and the disappearance of bacteremia. The patient's condition rapidly improved, the leucopenia disappeared, the psychosis cleared and the pneumonic process resolved satisfactorily. Red blood cells were not observed in the urine and the blood N.P.N. value remained in the normal range. (Case data through the courtesy of Dr. Joseph F. Sadusk, Jr., Yale University School of Medicine.)

Effective blood levels of free sulfathiazole for severe staphylococcal infections should probably be higher than those sought in pneumococcal pneumonias, and concentrations of six to nine mgm per cent of the free form may prove optimal. The dose scheme should be adjusted to allow these concentrations. It must be remembered that both supportive and surgical measures are also necessary in the proper treatment of staphylococcal infections, and the indications for these are not altered by sulfathiazole administration. Adequate surgical drainage of purulent foci must be effected, because sulfathiazole does not by itself cure areas of such localized infections, merely acting to inhibit the invasive manifestations of the staphylococcal infection.

Sulfathiazole therapy has accounted for one of the rare instances of cure of *staphylococcal meningitis,* there being only approximately 13 cases of such recoveries recorded in medical literature. Sadusk and Nieelson (1940) administered sulfathiazole orally and its sodium salt intravenously to a patient with staphylococcus meningitis. In addition, the sodium salt was injected intrathecally as a 0.5 per cent solution in physiological saline. Despite the high alkalinity of the solution, meningeal irritation apparently was not produced. The patient made an uneventful recovery. Dietel and Kaiser (1940) also have reported an instance of recovery from staphylococcal meningitis as a result of sulfathiazole therapy.

Staphylococcal pneumonia and *empyema* may also yield to treatment with sulfathiazole. Blake and Sadusk (1940) observed a patient with pneumonia and empyema due to *Staphylococcus aureus* who responded well to sulfathiazole and was ultimately cured (five month period of observation with normal lung fields, except for thickened pleura, and normal renal function and urine findings). The empyema cleared with conservative management (repeated thoracenteses).

The local use of sulfathiazole in aqueous solution or cod liver oil suspension in the therapy of staphylococcal infections, such as *carbuncles, wounds, osteomyelitis,* etc., has been reported on favorably by Spink and Paine (1940).

Urinary Tract Infections. Several reports indicate that sulfathiazole may prove of distinct benefit in the treatment of *urinary tract infections* due to a variety of organisms. Pool and Cook (1940) used sulfathiazole in 15 patients and sulfamethylthiazole in 35 patients. The cases were unselected and the type of infecting microörganism varied. The dose of either compound was four grams daily, given in one gram amounts four times daily. The average blood level reached with this regimen was four mgm per cent. The concentration of the drugs in the urine varied from 17 to 222 mgm per cent. The urines of approximately 65 per cent of the patients were rendered sterile from the use of either thiazole compound, and the investigators concluded from their preliminary experience that the two chemicals are about as effective in the treatment of infections of the urinary tracts as are other derivatives of sulfanilamide. However, in the case of infections due to *Staphylococcus aureus,* the sulfathiazoles were definitely superior. Of five patients with staphylococcal infections of the urinary tract, four were treated with sulfamethylthiazole and one with sulfathiazole—the urines of all five becoming and remaining sterile. Sterile urines were also produced in two of five patients with urinary tract infections due to *Streptococcus faecalis* treated with sulfamethylthiazole, and in one of two patients given sulfathiazole. Those individuals with this infection who responded satisfactorily had urinary concentrations of the drug exceeding 150 mgm per cent. Complicating pathological processes in the urinary tract were observed to decrease the efficacy of therapy with the sulfathiazoles, a phenomenon which is likewise true for sulfanilamide and sulfapyridine therapy.

Satisfactory experience with sulfathiazole in urinary tract infections has also been reported by Culp (1940) and Colston (1940). Culp treated a series of 30 patients and noted that the microörganisms which could be eradicated by the drug were *Staphylococcus aureus* and *albus, Proteus, Escherichia, Aerobacter, C. xerosis,* and *alpha Streptococcus mitis*. In several of the patients cured, blood levels reached were only one mgm per cent. Colston has also reported promising results from the use of sulfathiazole for coccal infections of the urinary tract.

Miscellaneous Infections. Sulfathiazole has been employed for a number of miscellaneous infections but its exact therapeutic status in these awaits determination. It has been used with success in several different forms of *streptococcal infections*. Sulfathiazole appears also to be of value in the treatment of gonococcal infections, including *acute anterior gonococcal urethritis* (Colston, 1940; Ballenger and coworkers, 1940; Mitchell and coworkers, 1940). Available evidence suggests that sulfathiazole will prove to be as effective as sulfapyridine in various types of gonococcal infections, although Spink and Hansen (1940) found sulfathiazole to be less satisfactory than sulfanilamide or sulfapyridine in four patients with gonococcal arthritis. Banks (1940), in a preliminary communication, reported the successful use of sulfathiazole in a limited number of cases of *meningococcal meningitis*. Whether sulfathiazole penetrates into the cerebrospinal fluid in patients with meningitis to a greater extent than it does in normal individuals is not determined. Weilbaecher and Moss (1940) have observed improvement in three of four patients with *tularemia* given sulfamethylthiazole, two of whom had failed to respond to other sulfonamide drugs. Spink and Hansen (1940) record clearing of the blood stream of *Escherichia coli* following the use of sulfathiazole in two patients with bacteriemia.

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SECTION XIV

DRUGS ACTING ON THE BLOOD AND BLOOD-FORMING ORGANS

The years immediately following the discovery in 1926 by Minot and Murphy of the liver diet for the treatment of pernicious anemia witnessed a marked revival of interest in the field of blood diseases and their therapy. As a result, knowledge of the mechanisms of blood formation and destruction, the metabolism of iron, the pathological physiology of pernicious anemia, and the specificity of hematinic agents is decidedly more complete. The physician now has at his command many accurate procedures for the diagnosis of blood dyscrasias, and several specific drugs for their therapy. It is no longer permissible to prescribe these agents without ascertaining as nearly as possible the exact nature of the blood disorder. Proper treatment then rests upon a clear understanding of the pharmacological properties of hemopoietic drugs.

CHAPTER 60

DRUGS EFFECTIVE IN IRON-DEFICIENCY ANEMIAS

IRON AND IRON SALTS

Historical. The empirical use of iron in the treatment of anemia dates from ancient times. The calcined iron preparation of ancient Hindu medicine known as Lauha Bhasma was prepared by roasting sheets of iron, followed by maceration to a fine white powder in oil, whey, vinegar, cow's urine and milk. The Greek physicians employed iron for the cure of weakness, a prominent symptom of anemia, in the attempt to impart to the patient the strength of the iron. Indeed, it was believed that Mars, the god of war, had imbued the metal with strength, and the alchemists designated iron as *mars*. Patients with marked pallor were given drinking water in which old swords had been allowed to rust, and Celsus advised that enlarged spleens be treated by using the water in blacksmith shops in which white hot iron had been drenched. He claimed that animals drinking such water had abnormally small spleens.

Sydenham was probably the first physician to employ iron in medicine in a manner that would be approved today. In 1681, he wrote the following concerning the treatment of chlorosis, ". . . I comfort the blood and the spirit belonging to it by giving a chalybeate 30 days running. This is sure to do good. To the worn out or languid blood it gives a spur or fillip whereby the animal spirits which before lay prostrate and sunken under their own weight are raised and excited. Clear proof of this is found in the effect of steel in chlorosis. The pulse gains strength, the face (no longer pale and death-like) a fresh ruddy color." Sydenham prescribed "steel in substance" or "iron or steel filings steeped in cold Rhenish wine," the dose amounting to 0.5 to 1.0 gram of iron daily.

It was not until 1713, however, that Lemery and Goeffy showed that iron was present in blood (ash), and in 1746 Menghini demonstrated that the eating of foods rich in iron could elevate the amount of iron in the blood. In 1831, Pierre Blaud recognized the nature of chlorosis when he wrote that the malady "arises from a faulty formation of blood as a result of which the blood is an imperfect fluid or the coloring matter is so defective that it is no longer suitable for stimulating the organism and maintaining the regular exercise of its functions." Blaud recognized that failure in the treatment of chlorosis was due to the use of too small doses of iron, and reported the rapid cure of thirty patients by the use of large doses of the metal. Blaud's original pills consisted of a mixture of equal parts of ferrous sulfate and potassium carbonate, and he gave a sufficient amount to yield a dose of from 0.4 to 1.6 grams of ferrous carbonate daily. This would be considered adequate therapy today. For many years, Blaud's nephew distributed throughout the world the "veritable pills of Doctor Blaud." The Blaud's pills incorporated in the U.S.P. and B.P. differ somewhat from the original both in composition and recommended dose.

In 1832, Födisch reported that the iron in the blood of chlorotics was greatly reduced, and ten years later, with the advent of methods for properly examining the blood, Andral and associates noted that iron therapy caused an increase in red blood corpuscles in anemia. Until the middle of the last decade of the 19th century, iron therapy of anemia followed the principles enunciated by Sydenham and Blaud, and was comparable to modern practice. At that time, the teachings of Bunge, Quincke, von Noorden and others caused a radical departure in the use of iron in anemia, and it came to be accepted either that the metal was not absorbed in the inorganic form or that only small doses were necessary. The clinical failure of small ineffective doses soon brought discredit on the value of iron therapy, and it was not until the end of the second decade of the present century that the lessons taught by the physicians of old were relearned (Haden, 1939). One need only compare the doses for iron given in the U.S.P. X with those in the U.S.P. XI in order to appreciate the change which has occurred.

The only important use of iron in modern medicine is in the treatment of iron-deficiency anemias. The administration of iron to patients with normal blood values serves only to increase the "reserve iron" of the body, and not to increase the red cells or hemoglobin above their normal physiological limits.

Distribution and Types of Iron in Nature. Iron is widely distributed in the animal body where it exists in several combinations, some of which are more or less firm and non-ionizable. Iron is found, for example, in the chromatin of all tissue cells, and is especially prominent in the hemoglobin of red blood cells and in the blood-forming and blood-destroying organs. Also, the metal is a necessary constituent of tissue oxidases, and plays an indispensable rôle in several of the enzyme systems of the organism.

"Organic" and "Inorganic" Iron. The distinction between organic and inorganic iron is at best somewhat elusive. The importance formerly attached to this distinction, however, is of considerable historical interest and deserves brief consideration.

"Inorganic" Iron. Iron in inorganic combination exists in the ionic form in solution, is dissociable by electrolysis and gives the customary iron reactions. Whether the iron is combined with an organic or inorganic anion is immaterial. In this sense, even iron albuminate is in the inorganic group. Indeed, most available forms of iron are inorganic. Many foods irons, formerly thought to be organic, are now considered to contain iron in ionizable combination.

"Organic" Iron. Iron in organic combination exists in the masked or non-ionic state. The metal occupies a non-dissociable and integral part of the molecule. The usual tests for the element are negative until the iron is liberated by partial destruction of the molecule. Examples of such organic combinations of iron are hemoglobin and cytochrome and some food irons which contain the metal in the form of heme compounds or in combination with certain nucleoproteins.

It was staunchly claimed for many years that inorganic iron could not be used by the mammalian organism for the building of hemoglobin. The prejudice against the idea that inorganic iron could be utilized in blood formation was in part due to the prevailing belief that inorganic substances could not contribute to the building of protein by the animal body. Inorganic iron was thought to be unabsorbed by the gastro-intestinal tract; but when the intestinal absorption of inorganic iron was unequivocally proved, it was argued that this form of iron was not converted into hemoglobin. When inorganic iron was shown to increase the hemoglobin in anemia, it was contended that it acted only by virtue of stimulating a better utilization of organic iron.

It is almost universally accepted today that inorganic iron is absorbed, assimilated and converted into hemoglobin in a manner precisely like that for organic iron, and that medicinal inorganic iron is far superior to food iron in causing a rapid blood response in anemia. All forms of iron, even metallic iron, can be assimilated. The attempt is still made, however, to promote organic iron preparations as superior in the treatment of anemia. A possible reason for the delay in admitting the superiority of medicinal inorganic iron was the disappearance of chlorosis, the syndrome in which iron therapy was most dramatic. Furthermore, the failure of iron to benefit patients with pernicious anemia and other anemias not due to iron deficiency, as well as the lack of knowledge concerning proper dosage, tended to confuse the status of iron therapy.

Absorption, Fate and Excretion of Iron. *Absorption.* Early studies seemed to show that iron did not traverse the intestinal wall, because the amount found in the feces approximated that taken in the food when analyzed by the inaccurate methods then available. By the use of fistulas at various levels of the intestinal tract, it was later demonstrated that iron is absorbed mainly in the duodenum and upper jejunum, and also in progressively decreasing amounts in the succeeding portions of the jejunum and ileum.

Iron is apparently absorbed directly through the cells of the intestinal mucosa, and by the use of proper staining technics, the metal can be demonstrated within the cells. This intra-epithelial mechanism suggests that iron absorption is a function of living cells. Inorganic as well as organic iron is absorbed, the latter first being changed by the intestinal juices in large part to the ionic form.

Absorption of iron probably does not occur from the stomach, but the gastric juice is important in changing metallic iron or its salts to chlorides. Before absorption, the gastric and intestinal juices may convert all forms of iron into inorganic iron, presumably into ferrous salts. Even the iron in hemoglobin and its derivatives, when fed orally, must first be broken down into ionizable iron in the gastro-intestinal tract.

It is now well established that both ferrous and ferric iron are clinically beneficial in iron-deficiency anemias. However, there is some evidence that only the salts of bivalent iron are absorbed in adequate quantity. Should this prove true, the clinical efficacy of ferric salts would depend in large part on their being changed to ferrous compounds in the intestinal lumen.

A number of factors determine the extent of absorption of iron and hence its ability to take part in hemoglobin formation. Ionization, though important, is not always a deciding factor. For example, in experimental anemias, ferric chloride, a highly ionizable salt, is poorly utilized whereas the iron in liver may be utilized to the extent of 45 per cent on oral feeding. The amount of iron salt fed is another factor, because at low dose levels a much higher percentage of the amount given is utilized than at higher dose levels (Table 56). Evidently, the rate of absorption is definitely limited even under optimal conditions.

The *acidity* of the contents of the stomach and upper duodenum favors iron absorption by preventing formation of insoluble iron compounds. Conversely, the alkalinity of the intestinal contents conspires against good iron absorption. For example, the use of alkali in anemic patients for the therapy of coincident peptic ulcer may markedly decrease the hemopoietic response to foods rich in iron (Kellog and Mettier, 1936), the same diet becoming effective for hemoglobin production as soon as the alkalis are stopped. In keeping with these facts, extensive gastric resections and achlorhydria lessen the efficacy of dietary iron. The presence of achlorhydria adversely affects the absorption of ferric salts more than ferrous salts, because the trivalent compounds then are not so readily converted to the ferrous state and form insoluble salts in the small intestine. Iron combines with amino acids, nucleic acids and phosphorous compounds in the intestinal lumen to form insoluble and therefore non-absorbable complexes. This is especially true of ferric salts, and may in part account for the larger doses they necessitate as compared with ferrous compounds.

The presence of normally secreted *bile* in the intestinal tract is an important conditioning factor in the absorption of iron. Anemic dogs with biliary fistulas utilize orally administered iron at only one-half the normal rate (Hawkins, Robscheit-Robbins and Whipple, 1938). However, an unexplained fact is that the feeding of bile orally does not improve utilization of the metal.

Fate. The iron absorbed into the epithelial cells of the intestinal mucosa reaches the circulation mainly by way of the intestinal capillaries and portal vein and not through the lymphatics and thoracic duct (Moore and coworkers, 1939). It is then transported in the blood to the various storehouses from which it may be mobilized for use in blood formation. The distribution and storage of iron in the body deserve special consideration.

Distribution and Storage. The distribution and storage of iron in the organism depend on the iron intake and the demand by the bone marrow for the metal. Although iron is present in all tissue cells, its concentration varies greatly in different organs. The several iron compartments of the body are as follows:

1. *Iron in red blood cells.* The largest fraction of the body iron is found in erythrocytes where it forms an essential part of the hemoglobin molecule, allowing the latter to serve as a respiratory pigment. Normally, the iron in hemoglobin constitutes approximately 55 per cent of the total body iron, the iron content of hemoglobin being 0.335 per cent. If the blood volume of an adult is taken as five liters and the hemoglobin level as 15.6 grams per 100 cc, the iron present in blood hemoglobin amounts to 2.65 grams. This value varies considerably, however, especially in patients with anemia or polycythemia. The iron in hemoglobin is present in the ferrous form. It acts as the link between the porphyrin and globin to form the metalloporphyrin-protein complex of hemoglobin. One atom of ferrous iron is joined with four molecules of pyrrol to constitute the metalloporphyrin.

2. *Non-hemoglobin iron in red blood cells.* A small fraction of iron exists in erythrocytes unassociated with hemoglobin. In amount, it exceeds that found in the plasma, and varies with individuals rather than with disease. It is uninfluenced by most conditions which affect other fractions of body iron. The function of this iron is unknown.

3. *Plasma iron.* A small amount of the total body iron is found in the blood plasma. The normal range for human plasma is approximately 0.050 to 0.180 mgm per cent. The plasma iron is apparently elevated in pernicious anemia and decreases during periods of active red blood cell formation, as for example during the reticulocytosis induced by liver therapy. The plasma iron increases even in normal persons after the administration of a single large dose of iron. The low values found in hypochromic anemia approach normal when medication with iron salts is instituted and may temporarily reach values of 0.500 mgm per cent. Plasma iron probably represents that fraction of iron which is in transport (Moore, 1937; Moore, Doan and Arrowsmith, 1937; Moore, Minnich and Welch, 1939).

4. *Muscle hemoglobin iron.* Still another fraction of body iron is found in striated muscle, chiefly in muscle hemoglobin. The latter is a non-circulating true hemoglobin which differs from blood hemoglobin in that its absorption bands are displaced to the red, in having a higher affinity for oxygen and a lower affinity for carbon monoxide, and in containing only one atom of iron per molecule (*see* review by Millikan, 1939). Differentiation from blood hemoglobin can also be made by specific precipitin tests. Like blood hemoglobin, when given parenterally, it yields bile pigments. The amount of muscle hemoglobin is lowered little, if at all, in severe anemias; but the concentration increases with exercise and age. The function of muscle hemoglobin is probably concerned with the transfer of oxygen from the blood to striated muscle, the pigment acting as a short-time oxygen store tiding the muscle over from one contraction to the next. The iron in muscle hemoglobin amounts to approximately seven per cent of the total body iron.

5. *"Parenchyma iron."* In addition to muscle hemoglobin, there is another iron fraction in striated muscle. It is likewise found in all other tissues and has been termed "parenchyma iron." This iron differs in form from the iron in muscle hemoglobin but is present in approximately equal concentration, varying from one to three milligrams per 100 grams of fresh muscle tissue. The function and nature of parenchyma iron are obscure, and it is not known whether it is in part or entirely of a hematin (cytochrome) nature. That parenchyma iron is of importance is suggested by the fact that the body holds to it tenaciously. Both muscle hemoglobin iron and parenchyma iron are inviolate iron stores of the body and are not drawn on for regeneration of blood hemoglobin regardless of the emergency or the severity of the anemia (Hahn and Whipple, 1936). Together these two fractions average approximately five mgm of iron per kg of body weight, and a 65 kg individual therefore has 0.325 grams of tissue iron unavailable for hemopoiesis.

6. *Visceral storage iron.* A final and extremely important fraction of the body iron exists as storage iron in certain organs rich in reticulo-endothelial cells, especially the liver, spleen and bone marrow, and occasionally in the kidney. Storage iron represents a reserve derived from the iron in the diet and the iron released from the continuous physiological destruction of red blood corpuscles. The amount of storage iron therefore varies with the sources of supply and also with demands made upon it for hemoglobin formation. Obviously, such demands are high during pregnancy, after hemorrhage, etc. The iron reserve in the viscera is used over and over again, and it is almost impossible to produce a severe anemia in an adult animal by limiting the iron intake.

The stored iron in contrast to parenchyma iron is not firmly bound and is easily available for use by the bone marrow. The total amount of storage iron has been variously estimated, but it is probably equivalent to an amount of iron contained in 250 grams of hemoglobin, that is, about 20 per cent of the total body iron. It is at least sufficiently plentiful so that a healthy adult in good nutritional condition can compensate for the loss of 50 per cent of his circulating red blood cells within a relatively short period without recourse to iron therapy.

Storage iron is transformed into hemoglobin only as needed. Excess intake of iron in the absence of increased demand merely augments storage in the viscera, where the metal remains until used or excreted. The concentration of iron in the liver, for example, may increase eight-fold as a result of large oral doses of iron. Mobilization from depots as a result of anemia or dietary restriction occurs readily. When the stores are exhausted, parenchyma iron is not utilized and growth and the production of blood hemoglobin suffer. If iron is fed to a patient with a severe anemia and exhausted iron reserves, the metal passes through the liver very rapidly to the bone marrow to be used by immature erythrocytes. It is not known whether iron under such conditions is first changed in the liver to heme precursors.

The *liver* also plays an important rôle in iron metabolism in fetal life and in the early months of infancy. The liver efficiently conserves more than 80 per cent of the iron released during the physiological blood destruction occurring in the first few weeks of post-natal life, and this iron supplies the major reserve for the building of new hemoglobin by the infant (Stearns and coworkers, 1937).

The *spleen,* due to its reticulo-endothelial system, is also important as a storehouse for iron and ranks second only to the liver. It conserves a large amount of the iron released from hemoglobin after internal hemorrhages or the intravascular crises of hemolytic diseases. It may even be more active in furnishing available iron than is the liver. Large doses of iron administered orally may increase the splenic store four-fold.

The distribution of iron as described has been accurately determined only in animals. Although the data for man are not nearly so complete, the values for the important fractions are approximately as follows (*see* Hahn, 1937; Heath and Patek, 1937):

Blood hemoglobin iron	2.65 grams
Available iron	1.32 *
Unavailable iron	0.33
	4.30 grams

* Obtained from clinical data rather than from organ analysis.

Excretion. On a normal diet, an adult excretes from 10 to 20 mgm of iron daily in the feces. Iron found in the feces is largely that which has escaped absorption, but also consists of iron excreted by the colon. This latter fraction represents the unconserved hemoglobin iron as well as that portion of absorbed iron which was unused for blood formation or storage. Iron excreted by the large bowel and found in the feces is in firm organic combination. It is claimed that the excretion continues during starvation, at which time it may even amount to eight mgm per day.

That the colon represents the main channel of excretion of iron from the body has been long accepted without serious question. Experiments on patients with ileostomies and isolated large bowels, however, do not support this teaching (Welch, Wakefield and Adams, 1936). Furthermore, studies of iron excretion employing transplants to the abdominal wall of the mucosa of the sigmoid of dogs fail to demonstrate any appreciable elimination of the metal by the colon (Maddock and Heath, 1939). It is hoped that by the use of the radioactive isotope of iron the problem of the elimination of the metal in the human intestine will be solved.

The urinary excretion of iron is negligible, and is not appreciably increased either by the oral administration of iron or the rapid liberation of hemoglobin by the destruction of erythrocytes with phenylhydrazine. The gastric juice may contain traces of the metal. Despite the important rôle played by the liver in the internal metabolism of iron, the bile contains only a small quantity of the element. This fraction is likewise uninfluenced in amount by an increased iron intake.

Radioactive Iron as an Experimental Tool. The technical difficulties in the study of the absorption, distribution, utilization and excretion of iron and its function in hemoglobin regeneration are many and often insurmountable (Hahn, 1937). By the use of the radioactive isotope of iron (radio-iron), however, many new facts may be brought to light concerning the metabolism of iron, because it is possible to "mark" the element and accurately to follow its fate in the body. It may well be that many of our present conceptions concerning the metal will require drastic revision.

The reports of Hahn, Bale, Lawrence and Whipple (1938, 1939), Hahn, Bale, Hettig, Kamen and Whipple (1939), and Hahn, Ross, Bale and Whipple (1940) support this possibility. These investigators, by the use of radioactive iron in dogs, have shown that when there is a distinct need for iron (as in anemia), a fair quantity of the metal passes from the gastro-intestinal tract to the blood stream. When the body reserves are ample, however, very little iron is assimilated, and the extent of absorption of iron in a non-anemic dog may be only $\frac{1}{70}$ of that in an anemic animal. The mechanism for this adjustment of the degree of absorption to the need for the metal is unknown. The percentage utilization of the radioactive iron increases as the dosage level decreases (and *vice versa*); but even when the smallest amounts of iron are given, gastro-intestinal absorption of the isotope is incomplete.

Peak absorption of iron occurs in anemic dogs between four and eight hours after feeding, that is, when the food is largely in the small intestine. At the end of 18 to 24 hours, the radioactive iron is practically all in the colon and no further absorption is demonstrable. The plasma content of radioactive iron is increased shortly after feeding and then drops off rapidly, suggesting that the plasma is the medium of transportation of iron from the intestinal tract to sites of utilization or storage. Radioactive iron appears in red blood cells with remarkable rapidity after oral feeding. Despite the fact that new erythrocytes do not enter the circulation of an anemic dog until three to five days after iron medication is instituted, radioactive iron in appreciable amounts is demonstrable in the corpuscles within four hours after feeding it. After 24 hours, the radioactive iron is present in considerable amounts and can be shown to be contained in crystallized hemoglobin, thus not being merely adsorbed to the erythrocytes. The iron is entirely converted into hemoglobin within four to seven days. However, when the rate of red blood cell production has been accelerated by feeding iron or by dietary factors, or when the dose of iron is very small, the standard anemic dog employed in the experiments can turn out as hemoglobin all of the absorbed radioactive isotope within two to three days. The investigators believe that the amount of new hemoglobin formed in anemic dogs with depleted iron stores is a quantitative measure of the total amount of iron absorption (*compare* page 1113), and that only small amounts of the iron are to be found in the storage depots.

In a study of the excretion of radioactive iron in dogs after the intravenous injection of the element as ferrous gluconate, the investigators cited found that the escape of iron from the body by way of the urine was negligible. The feces contained a remarkably uniform amount of radioactive iron, the dogs showing a steady low output of from 0.05 to 0.4 mgm per day, varying directly with body weight. The bile contained only a very small quantity of radioactive iron, but this amount was increased during phenylhydrazine-induced blood destruction. The conclusion is drawn from these preliminary studies that the iron content of the body is regulated through the control of absorption rather than excretion.

Obviously, many new horizons are presented by the use of radioactive elements in experimental and clinical studies in man.

Iron Requirements in Man. Careful balance studies show that a daily intake of five to eight mgm per day is required to maintain normal male adults in iron equilibrium. Inasmuch as approximately 75 mgm of iron are liberated daily by the physiological destruction of red blood corpuscles, the efficiency of conservation of iron approaches 90 per cent. Up to the age of the menopause, women require from two to four times more iron than do men, due to the loss of the metal in menstrual blood, balance studies showing a need as high as from 16 to 17 mgm daily in the experiments of Leverton and Roberts (1937). Young children require considerably more iron than do adults, amounting to 0.6 mgm per kg. Pregnant women also have a higher requirement, often 20 mgm per day being needed to keep in balance. It is estimated that each pregnancy requires approximately 400 mgm of iron. The normal diet of the average American adult contains from 10 to 20 mgm of iron, an amount which, as a rule, is sufficient for ordinary metabolic needs. The foods which mainly contribute to the iron content of the diet are red meats, green vegetables, whole wheat, egg yolk, carrots and fruit. It is these items that should be selected in prescribing a diet high in food iron.

The necessity for supplemental iron above that contained in the diet in the treatment of iron deficiency anemias may readily be appreciated after a closer inspection of some of the facts presented. The average normal adult with 100 per cent hemoglobin has a total of approximately 750 grams of circulating hemoglobin, containing approximately 2.5 grams of iron. In other words, each per cent of hemoglobin requires 25 milligrams of iron for its formation. The patient with an iron deficiency anemia, even if he absorbs and utilizes completely all the iron in his diet, is still unable to obtain the 25 mgm per day necessary to raise his hemoglobin one per cent per day, not an unreasonable rate. When in addition it is remembered that the dietary iron is by no means completely absorbed, and that the etiology of the anemia may be poor absorption or deranged utilization of the metal, chronic blood loss, or increased physiological demands, it becomes evident why it is so important to administer medicinal iron orally in order to obtain and keep normal blood values.

Available Preparations, Doses and Routes of Administration. There are many preparations of iron available for medicinal use in the therapy of anemia. Those most commonly employed in the United States are presented in some detail, other preparations being mentioned only briefly. All are inorganic compounds, the use of expensive organic preparations being obsolete. The significant feature common to all the following compounds is the large dose in which they must be given. Iron salts have many incompatibilities and should be prescribed alone.

Reduced Iron, U.S.P. Reduced iron contains not less than 90 per cent of metallic iron (B.P., not less than 80 per cent). It occurs as a very fine, grayish-black and lusterless heavy powder and has no taste or odor. Reduced iron is quite insoluble and must be dispensed in capsules or compressed tablets. The adult dose usually given in moderately severe anemia is one to one and one-half grams, two or three times daily. One-third to one-half of this amount may then be given after the patient's blood level has returned to normal, provided maintenance therapy is required. The small bulk of reduced iron is an advantage.

Iron and Ammonium Citrates, U.S.P. This compound is a mixture of iron citrate and ammonium citrate and contains 17.5 per cent of trivalent iron (B.P., contains 21.5 per cent). It occurs as translucent garnet-red scales or granules, which deliquesce in the air. The salt is odorless, but has a saline and mildly ferruginous taste. When well diluted in solution, the drug is practically tasteless. Iron and ammonium citrate is very soluble in water and can be given in solution. It can also be dispensed in capsules if these are kept dry. The dose for an adult with moderately severe anemia is four to eight grams daily, given in divided portions. After the desired hemopoietic response is obtained, one-half to one-third this amount may be prescribed if maintenance therapy is required. A drinking tube should be used to prevent staining of the teeth which may occur from solutions of this preparation. *Iron and sodium citrate* is also available and can be used in the same manner and dose as the ammonium salt.

Ferrous Sulfate, U.S.P., B.P. Ferrous sulfate (U.S.P.) contains approximately 36 per cent iron in the bivalent form, and consists of pale, bluish-green prisms or granules. In moist air, crystals of ferrous sulfate rapidly oxidize and become coated with a brownish-yellow, basic ferric sulfate, and must then not be used for medicinal purposes. The drug is never prescribed in solution, but is dispensed as pills or tablets, coated to protect them from moisture. The salt is mixed with glucose or lactose to protect it against oxidation. The dose of ferrous sulfate is smaller than that of reduced iron or ferric salts, and for moderately severe anemia averages one to two grams daily for adults, given in divided portions. Ferrous sulfate is perhaps the most widely used iron preparation in the United States.

Blaud's Pills (Ferruginous Pills, Pills of Ferrous Carbonate, Chalybeate Pills), U.S.P. These pills, introduced into medicine more than a century ago, contain ferrous carbonate, 0.065 gram each. Iron in the bivalent form is present in anhydrous ferrous carbonate to the extent of 48 per cent. The salt is relatively insoluble. The daily dose of *ferrous carbonate* for an adult with severe anemia is two to four grams, given in divided portions. Hence, if Blaud's pills are used, a large number of pills must be given, 30 to 60 a day. This may be decidedly inconvenient and patients complain of the large bulk. For moderate or mild anemias, the dose can be reduced to six pills (0.4 gram of ferrous carbonate) three times daily. The tablets should be fresh or they may pass through the intestinal tract unabsorbed. The B.P. also contains Blaud's Pills (Pill of Iron Carbonate) prepared somewhat differently from the U.S.P. preparation.

Another official preparation of ferrous carbonate is *Mass of Ferrous Carbonate,* U.S.P., which contains approximately 38 per cent of the iron salt. *Ferrous carbonate* as such may be dispensed in capsules containing 0.5 gram each, one to four capsules being given two or three times daily.

In addition to the preparations described, other compounds of iron are occasionally used. *Ferrous chloride* is a light-brown powder which is readily soluble in water. The metallic iron content is 44 per cent and the effective dose is three or four grams daily in divided portions, given in capsules containing 0.5 gram each. It may cause marked gastric disturbances. *Ferrous glutamate* has also been employed alone and in combination with ferrous chloride. It is a light-brown, fine powder, moderately soluble in water and contains 12 per cent metallic iron. The dose is three to nine grams daily, given in capsules to conceal the objectionable taste. *Ferric Pyrophosphate,* N.F., has been use for infants and has the advantages of being quite soluble, non-astringent and nearly tasteless. Soluble iron preparations dispensed in elixirs and syrups are useful in treating anemias in small children. Lastly, *ferrous gluconate* has been successfully employed in the therapy of anemia.

Side-Actions and Choice of Preparation. The preparations described allow the physician a fairly wide choice. The factors which should determine his selection are the patient's tolerance and the hematological response to the compound.

General intoxication from orally administered iron therapy is practically unknown. The iron salts used in anemias may cause gastro-intestinal reactions with gastric distress, colicky pain and diarrhea. These complaints are more prominent after ferric salts than after ferrous salts, and more common with the soluble than the insoluble preparations. It may take several days properly to adjust the dose of iron in order to circumvent gastro-intestinal symptoms. The patient should be forewarned concerning the possibility of cramps and diarrhea which, for example, occur in about one of every three persons who receive iron and ammonium citrate. If distress is experienced, the iron should be omitted for a day or two, after which it may be started again in smaller doses, the amount being gradually increased to the limit of gastro-intestinal tolerance. A few patients experience malaise after iron and ammonium citrate. Others cannot tolerate the double salt in any therapeutic dose and must be given a different iron preparation. Reduced iron is less disturbing than the ferric salts but even it may cause unpleasant intestinal side-effects. Constipation may occasionally occur from the use of metallic iron, but this is not common, and liquid petrolatum is usually effective in controlling it.The ferrous salts are considerably less irritating to the intestinal tract. This is especially true of ferrous sulfate, due in part at least to the smaller doses used. Diarrhea may occur in some patients with sensitive alimentary tracts, but a slight degree of constipation is perhaps more common.

Iron preparations are given after meals in order to lessen gastro-intestinal irritation. When a solution of iron and ammonium citrate is selected as the preparation of choice, a drinking tube should be used to prevent staining of the dental enamel. Iron medication colors the feces black and may interfere with the ordinary tests used for detection of occult blood in the stools.

The choice of preparation also largely depends on the blood response of the patient. Theoretically, almost any iron preparation given in sufficient amount should be effective in iron-deficiency anemias. In clinical practice, however, it may be impossible to give an adequate dose of a particular preparation due to the side-reactions mentioned. A few cases may be found refractory to any form of oral iron therapy. This is especially true of patients with malignant growths, chronic infection or chronic hemorrhage. Patients who are apparently refractory occasionally respond satisfactorily when the dose of iron is increased or the preparation is changed. There is no evidence of *tolerance* to iron after long continued use.

Efficacy of Various Iron Preparations in Relation to Dose. Iron preparations differ in the absolute doses needed to produce adequate responses in hypochromic anemias. This difference represents a variation in utilization, and the iron salts have been compared with each other in this respect by several investigators. The results of such studies are shown in Table 56.

The amount of iron utilized daily is calculated by the observed rise in hemoglobin values. A one per cent rise in hemoglobin represents an iron utilization of approximately 25 mgm. The iron content of the ingested salts is known and thus the percentage utilization of the iron in the different drugs can be calculated

TABLE 56

COMPARISON OF IRON PREPARATIONS IN RESPECT TO THEIR UTILIZATION IN HYPOCHROMIC ANEMIAS†

COMPOUND	DAILY DOSE	METALLIC IRON CONTENT OF DAILY DOSE	DAILY UTILIZATION OF INGESTED IRON	
	Grams	Mgm	Mgm	Per Cent
Ferrous Sulfate (Anhydrous)	0.5*	180	27.2	15.1
Mass of Ferrous Carbonate	2.0*	330	25.0	7.6
Iron and Ammonium Citrates	6.0*	1000	23.0	2.3
	3.0	500	14.1	2.8
	1.0	170	18.6	10.9
Reduced Iron	3.5*	3000	23.1	0.77

† Compiled from data of Brock and Hunter (1937), and Fowler and Barer (1937, 1939).
* Average doses necessary to allow approximately one per cent hemoglobin rise per day during period of study.

and compared. The absolute amount of ingested iron needed to produce the same rise in hemoglobin varies with each preparation. Apparently reduced iron has the poorest utilization and ferrous sulfate the best. It must not be inferred that these facts alone are a valid basis for a selection of drug, because all iron compounds are effective if given in sufficient amount. Nor must it be assumed from the low percentage utilization that small doses are as effective as large doses. Abundant clinical experience shows that this is not the case. Large doses succeed where small doses fail, especially in patients with hypochromic anemia and achlorhydria.

Fate of the Absorbed Iron. Table 56 emphasizes sharply that only a small percentage of the ingested iron is utilized for hemoglobin regeneration, and the question is legitimately raised as to what becomes of the iron which is not utilized. It is conclusively established that most of the orally administered iron is lost in the stool. It has been pointed out that ferrous salts are probably more readily absorbed than ferric salts, and this fact is reflected in the figures for their percentage utilization. But do these differences in absorption entirely account for the differences in utilization? Several investigators (Brock and Hunter, 1937; Fowler and Barer, 1937, 1938, 1939) report a wide discrepancy between the amount of iron retained in the body after absorption, and that utilized for new hemoglobin. Iron balance studies were made on patients with hypochromic anemia receiving either iron and ammonium citrate or ferrous carbonate in large oral doses. It was found, for example, that if the ingested iron ammonium citrate is taken as 100 per cent, the average figure for retained iron is calculated as 30 to 35 per cent, and the iron utilized for blood formation as only two per cent. This would indicate that 15 times as much iron is retained as is used for new blood pigment. Also, there is no direct correlation between the amount of iron retained and the increase in hemoglobin. The amount of iron retained but not used for building hemoglobin may even reach six grams in an experimental observation period, and this is more than twice the amount of iron in the entire blood.

These results are in keeping with those of Widdowson and McCance (1937) who studied the intake and output of iron in healthy men and women. On a dietary iron intake of six to nine mgm daily, the subjects remained in balance. When this was increased to 12 to 16 mgm daily, iron balance was similarly maintained. When one gram daily of medicinal iron in the form of iron and ammonium citrate was administered, however, a net retention occurred over a period of a few weeks of from 1.5 to 5.0 grams of the metal. Subsequently, without the elimination of the previously retained iron, the subjects were in iron balance when returned to diets low in the element. Fowler and Barer (1938) have likewise demonstrated that in patients with pernicious anemia, myxedema and lead poisoning, conditions in which an iron deficiency is thought to play no part in the anemia, the oral administration of iron results in the retention of from 25 to 34 per cent of the metal, just as in cases of hypochromic anemia.

It is likely that in patients with hypochromic anemia a part of the retained iron may go to replenish the depleted iron stores of the body, but this still leaves a large fraction unaccounted for. Under pathological conditions, such as hemochromatosis, more than 50 grams of iron may be deposited in the tissues. Apparently this abnormal type of deposition does not occur in patients on iron therapy, for pigmentary cirrhosis is not encountered. The ingestion of unnecessarily large amounts of iron, however, may not be without harm in infants, inasmuch as Elvehjem and coworkers (1935) have shown that in growing animals large doses of the metal interfere with the assimilation of phosphorus and may lead to severe rickets.

That all of the retained iron cannot be utilized seems to be indicated by the frequent clinical observation that when a patient with idiopathic hypochromic anemia, who is also bleeding, stops his large oral doses of iron, the anemia promptly recurs despite the ample amounts of iron retained from the previous medication.

It has been suggested that human iron balance studies such as those cited may involve a basic error in that iron may be adsorbed to the intestinal mucosa during the observation period, and hence a higher figure is obtained for retained iron than is actually the case. Whether or not this is true, one is forced to conclude that only a part of the absorbed metal is put to physiological use, and that the rate of hemoglobin formation can be employed only as an index of the amount of absorbed iron that is utilized, not as an index of the amount of ingested iron that is absorbed. Experiments with radioactive iron should serve to clarify the problem of the fate of the absorbed iron (page 1109).

Iron by Injection. Iron may also be given by intramuscular injection, the only permissible parenteral route. Such therapy is rarely needed and is resorted to only after the oral route has been given an adequate trial. The practice of giving by injection minute amounts of iron usually with arsenic in the belief that the patient is benefited in any manner other than psychic is irrational. In contrast to the safety, efficacy and cheapness of orally administered iron, the metal given by injection in painful, expensive and sometimes dangerous.

Indications. In an occasional patient with severe diarrhea or with a large resection of the intestine, it may be necessary temporarily to resort to the parenteral route for the administration of iron, if it has been demonstrated that the oral use of iron is ineffective. Rarely a patient will be encountered who cannot tolerate iron by mouth in any effective amount, or who refuses to take oral medication. Under such circumstances, the metal may justifiably be given by injection.

Preparations and Route. There are several preparations available for parenteral injection. *Green Iron and Ammonium Citrates,* U.S.P., may be given in doses of 0.06 gram two or three times daily, the largest permissible single dose being 100 mgm. The preparation is available in sterile solution in ampules. The B.P. contains a similar injectable iron preparation (Injection of Iron). *Ferrous gluconate* is also suitable for injection, and appears to be less toxic than the citrate salt. *Iron adenylate* has also been advanced as a soluble, stable and nontoxic preparation for intramuscular administration.

Reactions. Intramuscular injections of the green iron and ammonium citrates are often painful and occasionally may be dangerous. Immediate reactions of nausea and vomiting, fall in blood pressure, and pallor may occur, but as a rule are transitory. The gluconate and adenylate preparations are apparently free of these effects.

Efficacy. It is estimated that 32 mgm of iron and ammonium citrates given parenterally are the equivalent of one gram of the salt taken orally (Heath, Strauss and Castle, 1932). An injection of 0.1 gram of the salt supplies only 16 mgm of metallic iron. Even if this were completely utilized, it would permit the manufacture of only 0.6 per cent hemoglobin. A single daily dose for a month would therefore raise the hemoglobin only 20 per cent at best. There is little doubt, however, that iron by the parenteral route is efficiently utilized for building hemoglobin (Whipple and Robscheit-Robbins, 1936; Pohle and Heath, 1939). Clinically, however, the cost, pain and reactions make this route inadvisable except under the special circumstances already noted. It cannot be assumed that parenteral iron therapy is clinically more effective than iron given orally, and Heath and Patek (1937) in their review on hypochromic anemias state that ". . . the authors have not as yet observed a single case in which iron given by injection succeeded in promoting blood formation when by mouth it had failed to do so."

Use of Iron in Anemias. It may be categorically stated that iron is of value only in those anemias which have a low color index, that is, in hypochromic anemias. Any anemia with a color index below 0.6 is an iron deficiency anemia, with the rarest exceptions. In the presence of an iron deficiency, not only is hemoglobin formation impaired, but the hypochromic erythrocytes are usually smaller than normal. Thus, both the mean corpuscular hemoglobin and the mean corpuscular volume are low. The efficacy of iron therapy depends upon the actual need for the element. Normochromic and hyperchromic anemias are unresponsive to iron therapy. These facts indicate that a deficiency is being corrected by iron. The exact mechanism of iron utilization in the bone marrow is unknown, but it is quite certain that iron acts purely as a necessary constituent of the hemoglobin molecule and does not exert any "stimulating" effect on erythropoietic tissue. In the absence of anemia, an excess of the metal does not influence hemopoiesis.

Hypochromic anemias are most often due to chronic blood loss, the common sites of this loss being the gastro-intestinal and urinary tracts, and the uterus. For example, a woman who loses 50 cc of menstrual blood each month loses 300 mgm of iron yearly. In many other patients, however, iron deficiency anemias are due to a deficiency in iron intake. At certain times in life the iron requirements are increased, these being in infancy and childhood, at puberty (especially in girls), during pregnancy, and in females late in menstrual life or at the menopause. Iron deficiency anemia is particularly likely to occur at these periods unless the dietary iron is adequate or supplementary iron is provided.

Anemias due to an iron deficiency yield readily to iron therapy. Some of the most dramatic results are seen in patients with chlorosis or with idiopathic hypochromic anemia; but the hypochromic anemias of infancy and childhood, pregnancy and chronic blood loss also respond satisfactorily. In pernicious anemia, after a satisfactory hemopoietic response to liver therapy has occurred, the color index may fall to normal or below as the blood values rise. In addition to continued liver therapy, iron should be prescribed if an iron-deficiency phase develops. One is not justified in using mixtures of iron and liver (page 1135). On the contrary, specific medication is used for definite purposes, and the character of the anemia determines the type of therapy.

In patients with hypochromic anemia and achlorhydria, *Diluted Hydrochloric Acid,* U.S.P., may be given with meals, in doses of from two to eight cc diluted well with water and taken through a drinking tube to protect the enamel of the teeth. The gastro-intestinal complaints incident to the achlorhydria are ameliorated; but the administration of hydrochloric acid does not appreciably increase either the retention or utilization of medicinal or dietary iron (Barer and Fowler, 1937), despite the fact that achlorhydria may decrease the retention of dietary iron. When the therapeutic dose of the metal is adequate, retention of iron is usually satisfactory despite achlorhydria.

Exactly how long medication with iron need be continued is determined by the hemopoietic response obtained and by the nature of the individual case, especially in regard to the etiology of the anemia. Iron therapy is sometimes curative, but more often it is only symptomatic.

The *cost* of medication with iron is small when compared with the expense of liver therapy in pernicious anemia, and varies between one-half and three and one-half cents daily.

Response of Hypochromic Anemias to Iron Medication. The response obtained to iron in hypochromic anemia is directly proportional to the severity of the anemia. In uncomplicated cases of moderately severe anemia with hemoglobin values of 50 per cent or under, the *hemoglobin* should rise 1.0 per cent or more per day, or 1.0 gram per cent weekly for three or four weeks (Heath, Strauss and Castle, 1932). The rate of hemoglobin formation slows as the hemoglobin value approaches normal. For example, in a patient with a 65 per cent level of hemoglobin, a rise of 0.5 per cent per day is optimal. The *red blood cells* naturally increase more slowly than does the hemoglobin. As the hemoglobin value approaches normal, the red blood corpuscles may temporarily reach a level of six million per cubic mm. A rise of one-quarter of a million erythrocytes per week is a satisfactory response for a patient with a hemoglobin level in the vicinity of 50 per cent. The *reticulocytes* also increase in number and may become elevated within three days after iron therapy is started. The height of the reticulocyte response is inversely proportional to the hemoglobin value. With hemoglobin levels of 20 per cent, reticulocyte peaks of from eight to 16 per cent are seen; with levels of 40 per cent, reticulocytes reach heights of from four to 12 per cent; when the pigment value is 60 per cent, the peak value for reticulocytes falls to a level of from two to six per cent. The reticulocyte response is neither as regular nor as marked as that seen in pernicious anemia following liver therapy.

Maximal responses to iron occur during the second to fourth week of treatment. Several factors may complicate the response and render the metal less effective, such as infections, intoxications, chronic nephritis, hypothyroidism, cirrhosis of the liver, vitamin C deficiency, etc. Inasmuch as approximately one of three patients with severe hypochromic anemia may have chronic cystitis, infection of the urinary bladder is a common cause of a poor response to iron medication. These complicating factors require correcting before iron therapy will yield best results.

Not only does iron improve the blood picture, but it also relieves the menorrhagia, soreness of the tongue, dysphagia, dystrophy of the nails and skin, and fissuring of the angles of the lips which often characterize hypochromic anemia in women.

The main features of the hemopoietic response to iron in hypochromic anemia appear in Figure 103.

Other Therapy in Hypochromic Anemias. Other therapeutic measures available in patients with iron deficiency anemias are blood transfusions, an adequate diet, hydrochloric acid for the symptoms of gastric anacidity, and, most important, the search for and removal of the cause of the anemia, if this is possible. Copper does not significantly increase iron retention or utilization in hypochromic anemia in adults when adequate doses of iron are employed.

Actions and Uses of Iron Other Than Hematinic. The soluble salts of trivalent iron are protein precipitants, and are capable of producing astringent and irritant effects on the skin and mucous membranes. For these effects, they are occasionally used in the treatment of skin disorders. *Solution of Ferric Chloride* (U.S.P., B.P.) and *Solution of Ferric Subsulfate* (N.F.) are employed locally on the skin. However, when solutions containing iron salts are applied to eroded skin areas, as in ivy poisoning, permanent pigmentation may occur and their use is therefore not advisable in vesicular, bullous or exudative dermatoses (*see* Traub and Tennen, 1936; Sutton, 1937). *Tincture of Ferric Chloride* (U.S.P.) is occasionally diluted and used as an astringent gargle.

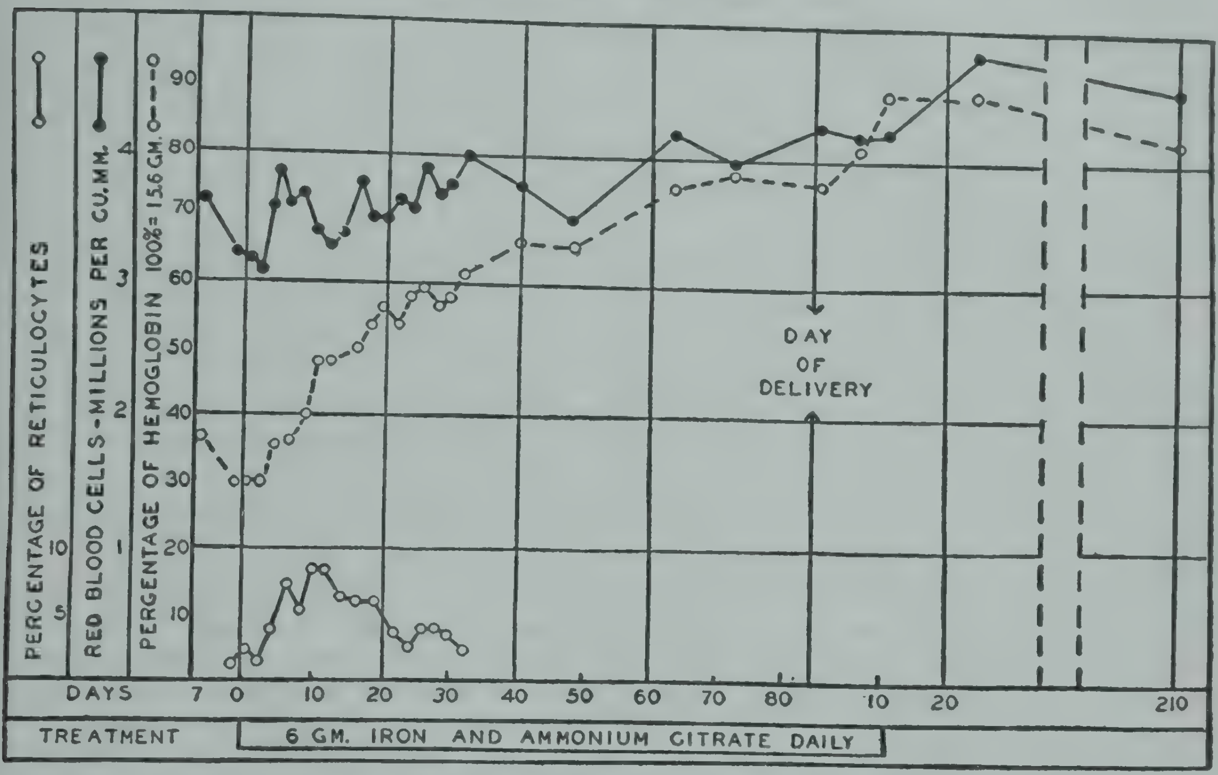

FIGURE 103. *The response of a patient with hypochromic anemia to iron therapy.*

Pregnant woman, 85 days antepartum, iron deficiency anemia, achlorhydria. Note the rapid and continued response to therapy with six grams of iron ammonium citrate daily. The increase in hemoglobin is characteristically more rapid than that of erythrocytes, and the reticulocyte response shown in the chart is adequate. Also observe that a satisfactory blood picture is maintained without therapy following delivery. (After Strauss and Castle, 1933. Courtesy of the *American Journal of the Medical Sciences.*)

COPPER

It is generally recognized that copper is universally distributed in animals and plants, but the full biological significance of the element is not known. Particular interest centers on the function of copper in the formation of hemoglobin and its possible systemic use in clinical anemias. The local actions and uses of copper salts in medicine are discussed elsewhere (page 861).

Distribution and Function of Copper in Nature. Although copper is ubiquitously distributed in water and soil and hence in living tissue, it is found especially concentrated in certain types of plant and animal cells. Yeast cells and many microorganisms appear to require copper for their metabolism. Copper is probably necessary for plant growth, but the type of copper compound present is unknown. Copper is associated in some manner, probably catalytic, with the formation of chlorophyl.

Starting perhaps with the demonstration by Bodansky (1921) that copper is a normal constituent of the human brain, being present to the extent of 3.6 to 6.0 mgm per kg, it has been established beyond doubt that copper is present in all animal tissues. Two naturally occurring pigments in which copper is an essential part of the molecule are *hemocyanin* and *turacin.* Marine animals such as *Mollusca* and *Crustacea* contain copper in their blue pigment, hemocyanin, which is functionally similar to the hemoglobin of red-blooded animals in being capable of forming a loose combination with oxygen. Turacin is a brilliantly red-colored pigment (copper uroporphyrin) found in the feathers of a certain species of bird, especially the African Turaco bird.

Absorption and Fate of Copper in Man. Copper is absorbed from the intestinal tract of man, but the factors controlling this assimilation are poorly understood as compared with iron, calcium, phosphorus and other dietary essentials. Copper is present in small amounts in all tissues of the body. The blood contains about 0.14 mgm per 100 cc, the major fraction being in the erythrocytes (Elvehjem, 1935; Sachs and associates, 1937). The serum copper is bound to protein to form copper-protein complexes (Keilin and Mann, 1939; Salomon, 1939), and in many forms of anemia the level of serum copper varies indirectly with the iron level of the serum.

The copper content of the liver and spleen is relatively high. These organs show a marked increase in copper as the amount of iron stored decreases, as in anemia (Hahn and Fairman, 1936). When the amount of copper in the diet is increased, copper is stored in the body, especially in the liver. For example, the liver copper in rats may be enhanced twenty-fold by the addition of copper to the diet (Lindow and coworkers, 1929). Normal levels are regained within a brief period after the cessation of copper feeding. Excretion of the element occurs in the urine to the extent of about 0.1 mgm per liter. Both cow's and human milk contain copper, the former averaging 0.15 mgm per liter.

Copper in Food. Daily Intake and Requirements. All foodstuffs contain copper but in varying degree (for exact figures, *see* the publication of Lindow, Elvehjem and Peterson, 1929). In descending order of their copper content may be listed nuts, dried legumes, cereals, dried fruits, poultry, fish, animal tissues, green legumes, roots and tubers, leafy vegetables, fresh fruits and non-leafy vegetables. Although a few forms of dietary copper are not available for use by the animal organism, unavailability of dietary copper is apparently of little practical importance in hemoglobin regeneration (Schultze, Elvehjem and Hart, 1936).

The copper requirements of normal human beings are not yet reliably established. Daniels and Wright (1934) suggest that the diet of pre-school children should contain not less than 0.1 mgm of the metal per kg of body weight. The average dietary in the United States probably yields about 0.8 mgm daily for a child three to four years old and 4.8 mgm for an adult working man. It is extremely doubtful, however, whether a deficiency of copper ever exists, except perhaps in certain infants suffering from nutritional anemias.

Rôle of Copper in Hemopoiesis. Copper appears to be concerned with the utilization of iron in the formation of hemoglobin in mammals, and also to hasten recovery from certain experimental nutritional anemias. In itself, however, the element does not stimulate blood formation.

Copper in Experimental Anemias. Growing rats made anemic by subsistence on a milk diet do not respond to highly purified iron preparations; but when a small amount of inorganic copper is added to the iron, a striking and immediate hemopoietic response with recovery from anemia occurs (Hart, Steenbock, Waddell and Elvehjem, 1928). This basic demonstration of the importance of copper in hemoglobin regeneration has been abundantly confirmed and extended to anemias of other species including dogs, pigs and lambs. It seems that copper is specific in this regard and that other trace elements can not stimulate a better utilization of iron in nutritional anemias. For example, Waddell, Steenbock and Hart (1929) found that a combination of 12 trace elements (zinc, nickel, chromium, germanium, cobalt, lead, antimony, tin, cadmium, mercury, arsenic and manganese) was ineffective.

It must be emphasized, however, that copper allows a better utilization of iron in anemia only when there exists both an iron and copper deficiency such as occurs when milk alone forms the diet. In the majority of experimental and clinical anemias, no deficiency of copper exists. That the dog may represent a species which requires copper as well as iron to repair an anemia due merely to *bleeding* is suggested by the work of

Potter, Elvehjem and Hart (1938). Hahn and Whipple (1938), however, believe that there is no satisfactory evidence that a copper deficiency can be demonstrated in dogs or man.

Copper in Clinical Anemias. Clinical evidence concerning the rôle of copper in blood formation is contradictory. Inasmuch as a copper deficiency is unknown in man, conclusions must be based on observed hemopoietic responses in anemic patients to iron alone and to iron with supplemental copper. Such observations are complicated by the facts that the dietary copper may vary and all commercial medicinal iron preparations are contaminated with significant amounts of copper.

It appears that in certain nutritional anemias in infants, especially nurslings, copper in combination with iron gives better results than iron alone (Lewis, 1931; Josephs, 1931, 1932; Cason, 1934; Elvehjem, Duckles and Mendenhall, 1937; Hutchison, 1938). This is true only when the infants' dietary does not contain sufficient copper, as is the case with a milk diet.

In anemias of adults, the value of copper as a supplement to iron is decidedly less clear than in anemias of infancy. Most hematologists believe that the iron-deficiency anemias of adults need not be treated by the inclusion of copper, and that only an occasional patient obtains a better response when the metal is added to therapeutic preparations of iron.

Function of Copper in Hemopoiesis. Copper does not influence the absorption of iron but is concerned with the utilization of iron in hemoglobin formation. When the diet is copper-free, iron storage in the viscera is enhanced. When copper is supplied, a larger portion of the storage iron is utilized in blood formation (Cunningham, 1931; Josephs, 1932; Elvehjem and Sherman, 1932; Hutchison, 1938). Although copper appears to aid the mobilization of iron from storage, it remains to be shown that the point of attack is not the bone marrow itself. Copper conceivably can increase the rate of hemoglobin formation in immature erythrocytes, or decrease the rate of hemoglobin breakdown in mature cells.

Status of the Uses of Copper in Clinical Anemias. The available facts suggest that, with the exception of certain cases of hypochromic nutritional anemias in very young infants, copper is not necessary for the therapy of clinical anemias. Even in anemias of infants it is not indispensable. There is no clear evidence that anemias in adults require medicinal copper, and highly purified iron preparations free of copper appear to be quite as effective as the cruder preparations containing the metal. Hahn (1937) summarized the status of copper in clinical anemias as follows: "The amount of copper required is so small and its occurrence in foods so widespread, that from a practical standpoint there is no indication whatsoever for the inclusion of this element in anemia therapy. The possibility of a copper deficiency occurring in humans is exceedingly remote, if it exists at all."

The present tendency to use copper indiscriminately in anemias can only be deplored. The practice is encouraged by commercial firms who market preparations containing both iron and copper, or "shot-gun" mixtures of hematinic agents. In addition to the usual reasons why such mixtures should not be used by the physician (page 1135), another factor should be considered. Some authorities are inclined to believe that excessive storage of copper may eventually lead to hemochromatosis (Mallory, 1931). Although this danger of copper has been denied (Sheldon, 1934), the opinion often expressed that copper should be added to iron in the therapy of anemias because it may do good and cannot do harm does not make for clear medical thinking or rational therapeutics, and should not be countenanced.

Preparation, Dose and Route of Administration. The dose of copper for infants is approximately three mgm per day, given orally as the *copper sulfate* in solution in milk or fruit juice. The adult dose of copper sulfate is five to 10 mgm three times daily, taken orally in capsules. *Copper Sulfate (Cupric Sulfate)*, U.S.P., B.P., $CuSO_4 \cdot 5H_2O$, consists of deep blue triclinic crystals, or blue crystalline granules or powder, soluble in about three parts of water and possessing a nauseous metallic taste.

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CHAPTER 61

DRUGS EFFECTIVE IN PERNICIOUS ANEMIA AND ALLIED ANEMIAS

LIVER EXTRACT AND DESICCATED STOMACH

Minot and Murphy in 1926 made the epochal discovery of the efficacy of a diet of liver in the treatment of pernicious anemia. This fundamental observation, coming after the basic work in experimental anemia of Whipple, Robscheit-Robbins and their coworkers, and the subsequent contributions of numerous investigators, have completely revolutionized our knowledge of the cause and treatment of pernicious anemia, and the relation of the diet, gastric secretion and the liver to normal hematopoiesis. Before considering the pharmacology of liver and stomach preparations as antianemic substances, it is necessary to review the pathological physiology of pernicious anemia and closely related anemias in order to obtain a clear understanding of the therapeutic problems involved.

Classical addisonian pernicious anemia, as understood at present, is a deficiency disease due to the lack of a specific substance found especially in liver. This substance, the exact nature of which is unknown, is as specific in the therapy of pernicious anemia as insulin is in diabetes mellitus. It has been called the antianemic principle (A.A.P.) and the term "liver-deficiency anemias" embraces a group of diseases resulting from the absence of this principle. Thus pernicious anemia may be viewed as a symptom-complex arising from a long-continued deficiency which results in definite pathological changes especially in the tongue, gastric mucosa, bone marrow and nervous system. The signs and symptoms which follow are those related to severe hyperchromic macrocytic anemia, such as weakness, shortness of breath, cardiac pain, slight icterus and edema; those related to the gastro-intestinal tract, such as sore, raw and smooth tongue (Hunterian tongue), dyspepsia and diarrhea; and those related to the nervous system, such as peripheral neuritis, posterolateral sclerosis, optic atrophy and psychosis. Thus anemia is only one of the many manifestations of the deficiency of the liver principle. Pernicious anemia is a fatal disease unless the deficiency is corrected, whereupon the fatal termination may be postponed indefinitely.

Steps Involved in the Formation and Utilization of the Antianemic Principle. These steps are important from the standpoint of understanding the genesis of pernicious anemia and at what points therapy may be directed. It is now generally agreed that at least five factors are involved in the elaboration and use of the substance or substances necessary for normal maturation of red blood cells and for prevention of the aforementioned signs and symptoms. These are as follows:

(1) An extrinsic factor contained in the food.
(2) An intrinsic factor contained in the gastric mucosa and secreted into the gastric juice.
(3) An interaction of the extrinsic and intrinsic factors in the gastro-intestinal tract to form an antianemic substance which is absorbed by the intestine.
(4) The storage of the antianemic substance by the liver, and perhaps its further modification in this organ.
(5) The release of the antianemic principle to the hemopoietic tissues and its utilization by the bone marrow in normal erythropoiesis.

These five factors deserve closer scrutiny.

1. *The Extrinsic Factor.* Much of our information concerning the rôle of the diet in the elaboration of the antianemic substance has been contributed by the basic work of Castle and his associates (1929, *et seq.*). Castle's observations have shown that there is a factor in food which supplies the necessary substrate with which the gastric juice reacts to form the precursor of the liver principle. The exact nature of this food factor is unknown. It is a widely distributed and thermostable substance which is abundantly present in autolyzed brewers' yeast, beef muscle, wheat germ, liver and liver extract, eggs, milk and rice polishings, and absent in casein and wheat glutein. The presence of the extrinsic factor in a food is determined by incubating that food with normal gastric juice. The resultant digestion product is then assayed in patients with pernicious anemia in relapse for its ability to cause a satisfactory blood response. Despite the fact that the extrinsic factor is especially abundant in those foods rich in the vitamin B complex, the factor is not identical with any of the known constituents of vitamin B.

Pernicious anemia is not due to a faulty diet, but it cannot be denied that a prolonged dietary deficiency may be a precipitating factor in some patients. Nor can one be certain that a deficiency in food intake may not in some way be related to the disturbances in gastric function characteristic of the disease. Furthermore, there is evidence indicating the importance of an adequate diet in both the prevention and therapy of the allied anemias of sprue and pellagra and the macrocytic anemias of the tropics. The extrinsic factor alone is ineffective in eliciting a therapeutic remission, although Wintrobe (1939) reported that dehydrated brewers' yeast fed orally to patients with pernicious anemia causes hematological responses. The chemical nature of the substance responsible for Wintrobe's results awaits identification. Heinle and Miller (1939) believe that the partial response they obtained from feeding yeast to two patients with pernicious anemia is the result of feeding an excess of extrinsic factor in the presence of greatly decreased but not completely absent intrinsic factor.

2. *The Intrinsic Factor.* Castle and his collaborators showed that the basic pathological change in pernicious anemia is the inability of the gastric mucosa to secrete a substance which they tentatively called the "intrinsic factor." Its chemical nature is undetermined, but there is evidence suggesting that it is a proteolytic enzyme (Taylor, Castle and associates, 1938). It is salted out by ammonium sulfate, is non-dialyzable, is not removed by Berkefeld filtration or destroyed by exposure to alkali, is inhibited at a pH below 3.5 but is active near 7.0, is destroyed at 70 to 80 C in one-half hour or by boiling for five minutes, and is inactivated by heavy metals. The secretion of the intrinsic factor is not dependent upon the ability of the stomach to form hydrochloric acid, and achlorhydria therefore is not necessarily associated with the loss of the intrinsic factor. The formation of the intrinsic factor is likewise dissociated from the secretion of pepsin both anatomically and physiologically. It is important, however, to recall that patients with pernicious anemia usually do not secrete pepsin and that with few exceptions they show a total absence of free hydrochloric acid. These facts seem to indicate a generalized and basic disturbance of gastric physiology involving the secretion of both enzymes and acid.

The nature of the gastric disturbance can only be surmised but it probably has an anatomical basis. A wide variety of gastro-intestinal defects has been reported at autopsy and from direct gastroscopic observations. Prominent among these are gastritis and atrophy of the gastric mucosa. However, there is nothing specific in the pathological changes which occur. Indeed, the chief histopathological lesions appear in the fundus of the stomach and not in those areas of the alimentary canal which are believed to secrete the intrinsic factor (Magnus and Ungley, 1938; Meulengracht, 1939).

The intrinsic factor is formed particularly by the pyloric glands of the stomach, but the duodenum and in some animals the upper part of the jejunum are also potent sources (Meulengracht, 1934, *et seq.*). The Brunner glands of the upper part of the small bowel are morphologically and developmentally identical with the pyloric glands, and together they form what has been called the "pyloric gland organ" or "pyloric gland system." It is clear from Meulengracht's investigations, adequately confirmed by the experiments of other observers, that the stomach, both histologically and functionally, is divided into two distinct parts—a fundus portion containing fundus glands with parietal and chief cells secreting hydrochloric acid, pepsin and rennin, and a pyloric portion containing large clear gland cells which apparently secrete the antianemic intrinsic factor of Castle. The known efficacy of powdered stomach or duodenum in the therapy of pernicious anemia is thus explained, as well as the fact that few patients with extensive gastric resections develop hyperchromic macrocytic anemia. The stomach, however, is the main source of supply of the intrinsic factor. Therefore, an anemia allied to pernicious anemia may occur in some patients with extensive gastric carcinomas, total gastrectomies or linitis plastica, as well as in those whose gastric mucosa has been extensively scarred by corrosives.

It has already been mentioned that the histological lesions found in the stomachs of patients with pernicious anemia are largely confined to the glands of the fundus rather than to the pyloric gland system which remains quite well preserved. This fact makes it clear why cessation of secretion of pepsin and hydrochloric acid occurs, but it does not explain why the intrinsic factor of Castle is inadequately secreted in patients with pernicious anemia, there being no histological basis for the reduced production of this factor. Meulengracht (1939) has advanced two hypothetical explanations which may account for the anomaly. The first is that the fundus gland system normally may act as a starter or pacemaker for the pyloric gland system, perhaps in a manner analogous to the stimulation of pancreatic secretion by secretin formed in the duodenal mucosa. The second possibility is that the normally secreted intrinsic factor meets unfavorable conditions in the small intestine due to lack of secretion of pepsin and acid by the stomach. As will be explained presently, the small intestine is the probable site of the interaction of the extrinsic and intrinsic factors of Castle. Both possibilities suggested by Meulengracht require further investigation.

It is possible to demonstrate the presence or absence of the intrinsic factor in a patient suspected of having pernicious anemia only by incubating his gastric juice with a potent source of the extrinsic factor and testing the resultant mixture for the interaction product as described. The technic is too laborious for clinical purposes, and the diagnosis of pernicious anemia therefore rests upon the clinical picture, blood morphology and achlorhydria. By the use of such a test, however, Goldhamer (1936) has shown that the intrinsic factor is not entirely absent in pernicious anemia but that a small amount is still detectable. The amount found is proportional to the total volume of gastric secretion, which is characteristically reduced in pernicious anemia. It is therefore not an absolute but rather a relative deficiency which conditions the occurrence of the disease. The concept of a relative deficiency is important because it indicates that a number of associated precipitating factors may combine to produce pernicious anemia. For example, in an individual with a given decrease in intrinsic factor, anemia may be precipitated by a faulty diet, infection or pregnancy, whereas another person with a similar reduction of intrinsic factor, under more favorable circumstances, may escape the disease for some time.

The final proof of the presence of a factor in the stomach necessary for normal blood formation has been presented by Wilkinson and his coworkers (1938). They found that an antianemic substance effective in pernicious anemia was obtained by the incubation of *normal human stomachs* with beef muscle, but that no such substance appeared when stomachs obtained from pernicious anemia patients in relapse or in remission were used. This agrees perfectly with the findings of Castle on the lack of secretion of the intrinsic factor in patients with pernicious anemia.

3. *Interaction of the Extrinsic and Intrinsic Factors, and the Absorption of the Interaction Product.* Both the extrinsic and intrinsic factors are ineffective when given alone but highly effective if administered after they have interacted. Little information is available concerning the nature of the interaction between the food and gastric factor. The relationship is probably that of an enzyme and a substrate, but the exact site of the interaction and the specific conditions controlling it are imperfectly known. Castle's later experiments make it highly probable that the interaction takes place not in the stomach but in the small intestine.

Absorption of the interaction product occurs from the intestinal tract, and a deficiency in absorption may result in anemia resembling pernicious anemia. One of Addison's original cases was that of a patient with ulcerative enteritis. There is no reason to suppose, however, that in classical pernicious anemia there is a disturbance of intestinal absorption, especially because most patients yield in some measure to therapy with liver by mouth. On the other hand, in the diarrheas of sprue and pellagra and in idiopathic steatorrhea, the occurrence of macrocytic hyperchromic anemia which often responds to the parenteral administration of liver extract suggests that faulty intestinal absorption is the cause. A similar conclusion can be drawn from occasional cases of macrocytic anemia occurring in patients with intestinal obstruction, ulceration or fistula, or extensive intestinal resection. The possibility of destruction of the antianemic principle in the intestine must also be considered.

Although an essential interaction between the extrinsic and intrinsic factors occurs in the alimentary tract, it is probable that only a preliminary step in the ultimate formation of the active principle of liver is accomplished at this stage. From the intestinal lumen, the interaction product is carried to the liver, where it is stored and probably further elaborated.

4. *Storage of the Antianemic Principle.* After absorption, the interaction product is stored primarily in the liver but also in certain other organs such as the kidney, brain and placenta, although potent injectable extracts are not obtainable from organs other than the liver. A high concentration is present in the liver of man and many domestic animals. The commercial source of liver extract is from pigs, cattle and horses. The storage of the antianemic principle is not essential for normal hemopoiesis for the liver may be devoid of the principle and yet pernicious anemia does not necessarily develop. This is clearly shown by the finding that the livers obtained from non-anemic gastrectomized swine (Goodman, Geiger and Claiborn, 1935) and from patients with marked hepatic cirrhosis but without addisonian anemia are lacking in the liver principle. Apparently the bone marrow can draw directly upon the blood for antianemic substance, and there may be other storehouses in patients with cirrhosis of the liver.

That patients with pernicious anemia lack the liver principle has been established by assaying the extracts of livers obtained at autopsy from individuals dying during a relapse. Livers obtained from patients in therapeutic remission at the time of death, however, have been found to contain the antianemic principle and therefore the defect is not an inability to store the substance but an inability of the gastro-intestinal tract to produce it.

The etiology of the *macrocytic anemia occurring in diseases of the liver,* especially cirrhosis, has been the subject of much dispute. The question involved is whether the anemia is related to pernicious anemia and due to an inability of an injured liver to store and metabolize the liver principle. Many patients with long-standing and marked hepatic cirrhosis, however, do not have macrocytic anemia, and those who develop it usually respond rather poorly to liver extract. More important is the fact that the bone marrow in hepatic cirrhosis shows a normoblastic type of hemopoiesis rather than the megalobastic hyperplasia which is pathognomonic of pernicious anemia. Macrocytosis alone is not diagnostic and may be caused by factors other than those related to the etiology of pernicious anemia. Finally, cirrhotic human livers have been assayed in pernicious anemia patients in relapse, and in several instances have been found to contain the antianemic principle (Schiff and coworkers, 1938). This suggests that macrocytic anemia associated with liver disease is not caused by failure of the liver to store the specific erythrogenic material.

5. *Release of the Antianemic Principle from the Liver and Its Utilization by the Bone Marrow.* The liver stores of the antianemic principle are drawn on by the hemopoietic organs for use in building normal blood cells. There is no evidence either that the release of the antianemic substances from the liver or its utilization by the bone marrow is at fault in classical pernicious anemia. Rather the erythrogenic material is never formed. However, in a syndrome described by Israëls and Wilkinson (1936, 1940) many of the classical features of pernicious anemia are present, especially the characteristic megaloblastic hyperplasia of the bone marrow. Inasmuch as the livers of such patients contain the liver principle as determined by clinical assay, and the syndrome is quite refractory to therapy with massive doses of potent liver extract, it appears that this disease is due to faulty utilization of the liver principle. Hence this anemia has been termed "achrestic" to signify lack of utilization. The marked refractoriness to therapy with liver extract occasionally shown by patients with pernicious anemia of pregnancy suggests that an "achrestic factor" may complicate the picture.

The Bone Marrow in Pernicious Anemia. The absence of the antianemic principle results in a characteristic and diagnostic megaloblastic hyperplasia of the bone marrow consisting of a maturation-arrest of primitive red blood cell precursors. The megaloblasts give rise to the typical hyperchromic and macrocytic erythrocytes seen in the peripheral blood, and represent cells pathognomonic of pernicious anemia. Due to the work of Hoffmann (1936) Dameshek and Valentine (1937), Jones (1937, 1938), Israëls (1939), and others, it now appears that the *megaloblast* is a pathological cell found only in pernicious anemia. The leukopenia and thrombocytopenia observed in this disease are also due to changes in the bone marrow resulting from lack of the antianemic principle. Examination of the marrow reveals an abnormal growth of leukocytes and megakaryocytes, and there occurs a maturation-arrest of white blood cell precursors as well as erythrocytes. This accounts for the "old" and large polymorphonuclear leukocytes with multisegmented nuclei which are seen in the blood smear. It is apparent that the liver principle is essential for all the hemopoietic functions of the bone marrow, that in its absence there occurs a panmyelopathy, and that the antianemic factor acts primarily on the stem cells of the bone marrow or perhaps on the reticulo-endothelial elements.

Response of the Bone Marrow in Pernicious Anemia to Liver Extract. Within a short time after the institution of specific therapy in pernicious anemia, the megaloblastic hyperplasia ceases, the pathological megaloblasts pathognomonic of pernicious anemia develop into reticulated and mature megaloblasts and in this manner are purged from the bone marrow and replaced by normal cells of the normoblastic series. Serial bone marrow biopsies in patients with pernicious anemia during the course of liver therapy show that the cellular changes start within twenty-four hours or less after the injection of liver extract. The misshapen giant neutrophilic leukocytes also vanish. As therapy and improvement continue, the characteristic hyperchromic macrocytic anemia, leukopenia and thrombopenia disappear. The patient under adequate treatment reveals no evidence of the disease either in the bone marrow or peripheral blood.

The Relation of Neurological Changes to the Antianemic Principle. Careful examination of patients with pernicious anemia reveals involvement of the spinal cord or peripheral nerves in 70 to 80 per cent. Cerebral changes occur in 60 per cent of all cases, and in some series the incidence of psychotic changes is 16 per cent. The cause of the neurological lesions, though not clear, is related to the absence of the antianemic principle. Whether the antianemic principle is multiple in character and contains one substance necessary for maturation of blood cells and another distinct factor necessary for the maintenance of the integrity of the nervous system is not known. Some investigators are inclined to believe that there are two components present in the intrinsic gastric factor, "neuropoietin" necessary for the nervous tissues, and "hemopoietin" necessary for the bone marrow; but the evidence on this point is not conclusive.

The efficacy of liver therapy in arresting or preventing involvement of the nervous system is beyond question. It does not appear that the anemia is the cause of the anatomical changes in the nervous tissues because the lesions may occur before anemia is evident. Furthermore, neural damage may continue to progress after the blood picture has been restored well toward normal. Lastly, severe anemia of non-addisonian character is rarely associated with lesions of the nervous system.

The Chemical Nature of the Antianemic Principle of Liver. Unfortunately, all attempts at the chemical isolation and identification of the active substance responsible for the therapeutic potency of liver extract in pernicious anemia have been unsuccessful. Many of the questions raised will not be solved until the liver principle is obtained in pure form. At present, the only acceptable method of testing for the presence of this substance is the expensive and tedious one of clinical assay in pernicious anemia patients in relapse.

In 1927, Cohn and his associates demonstrated that the active substance in liver is a water-soluble substance retained after precipitation of protein. This fraction is called the "fraction G" of Cohn and is the extract used orally in therapy as well as the starting point for the manufacture of the concentrated solutions used parenterally.

The available information concerning the chemical nature of the hemopoietically active fraction of liver is meager. The principle is thermostable at 100 C. at pH 5.0, is soluble in water and 70 per cent alcohol, and is not destroyed by hydrochloric acid or proteolytic enzymes. It contains carbon, nitrogen, hydrogen and oxygen, but phosphorus and sulfur are apparently absent. Highly purified active preparations give positive xanthoproteic and Hopkins-Cole tests. Such chemical and physical properties as have been elucidated suggest that the material is a peptide, the molecular weight of which is between 5000 and 10,000, as determined by the ultracentrifuge and passage through graded membranes. It does not contain thiamine, nicotinic acid or riboflavin.

Small amounts of highly purified preparations have been found to be therapeutically potent. For example, Laland and Klem (1936) have isolated a chemical fraction from liver extract which was found to be clinically effective by Strandell and associates (1936) in a dose of only 0.7 mgm, and Tschesche and Wolf (1939) described a highly active preparation which in a single dose of 40 mgm maintained a normal blood picture for at least four weeks. The last-named authors have described in detail the isolation and chemical properties of their fraction.

Absorption, Fate and Excretion of the Antianemic Substance. Absorption of the antianemic principle occurs from the intestinal tract, rectum and subcutaneous tissues. Approximately thirty to fifty times as much liver extract must be given orally as intramuscularly in order to obtain comparable clinical effects. The cause for the limited amount absorbed by the intestinal tract is unknown. Storage of the antianemic principle in the liver and other organs of the body has been discussed. It is also stored in the placenta and is easily capable of crossing this barrier to gain access to the fetus. The fate of the antianemic principle in the body is in part concerned with its utilization by the bone marrow for normal blood formation. Excretion probably occurs through the kidney, and a substance having hemopoietic potency can be isolated from the urine. For example, urine from a normal individual, when given rectally as a retention enema to a patient with pernicious anemia in relapse, produces a reticulocyte response and an increase in erythrocytes and hemoglobin. Furthermore, Wilkinson and coworkers (1940) demonstrated that the intramuscular injection of extracts prepared from the urine of normal humans and from patients with pernicious anemia in therapeutic remission was capable of inducing hemopoietic responses in patients with pernicious anemia in relapse. Similar active extracts could not be prepared from the urines of untreated cases in relapse. The exact relation between the active urinary principle and the antianemic principle of the liver has not been determined.

Classes of Available Antianemic Preparations. Whereas prior to the discovery by Minot and Murphy of the efficacy of liver the physician was faced with the problem of what to do for his pernicious anemia patients, today he is puzzled by the many available preparations for selection. One no longer has to rely on the inclusion of fresh liver in the diet. Various types of dry powdered extracts of liver for oral use are available, as well as solutions of liver extract. In 1930, solutions of liver extract sufficiently purified for parenteral administration began to appear. and this marked a great advance in the treatment of pernicious anemia, especially in desperately ill patients or those with neurological involvement. In 1929, Sturgis and Isaacs, and Sharp demonstrated that dried defatted hog stomach taken orally was as valuable as orally administered liver, and preparations of stomach are also employed in therapy. The introduction of liver-stomach concentrates for oral use soon followed. The chief advances in the development of new antianemic preparations have been the refining and concentrating of liver extract for injection with the object of increasing its potency so as to allow smaller volumes of solution to be given at less frequent intervals. Many investigators are of the opinion, however, that extracts which are too refined may lose certain essential factors present in less purified preparations.

Standardization and Assay. The lack of a chemical assay for antianemic preparations and the inability thus far to find a suitable laboratory bio-assay method necessitate standardization by clinical trial in pernicious anemia patients. The U.S.P. includes oral and parenteral liver preparations but does not describe the method of clinical assay. This is left to a special U.S.P. *Anti-Anemia Preparations Advisory Board.* Approved products must comply with the specifications of this Advisory Board. The B.P. contains preparations of liver extract for oral administration only.

Unitage. The U.S.P. has adopted a *unit* for expressing the potency of antianemic substances. The U.S.P. *unit* is defined as the amount of antianemic material which, when given daily by mouth or by injection to patients with addisonian pernicious anemia, has been shown in the opinion of the Advisory Board to have produced a satisfactory rise in reticulocytes and increase in erythrocytes and hemoglobin. It is evident that the amount of material constituting a unit is determined in terms of the hemopoietic response alone and this does not imply that such an amount is necessarily effective in the control of gastro-intestinal or neurological manifestations. The U.S.P. unit also does not imply that it represents the minimal amount of effective material which might produce a satisfactory response but merely signifies that the particular amount of material has produced such a response. U.S.P. units are therefore not interchangeable from one product to another and a patient maintained in good health on a given number of U.S.P. units of one preparation may require readjustment of dose when shifted to a different preparation.

Because, in the average case, material derived from about thirty times as much liver must be given by mouth to elicit the same hematological response as when given intramuscularly, the U.S.P. defines the unit as an *oral unit* or as an *injectable unit,* according to the intended method of administration of each preparation. Labels on products accepted by the U.S.P. must state the number of cc's or grams of material constituting a unit, and also whether the unit is oral or injectable. These two classes of units are obviously not interchangeable. Furthermore, the manufacturer cannot recommend a dose of less than one unit per day, regardless of whether medication is given daily or at longer intervals. The Advisory Board will not, for the present, assign to any preparation of injectable liver extract a strength greater than 15 units per cc because of the possibility that a loss of unknown factors of value in treatment of patients with pernicious anemia may occur in the process of concentration. It should be pointed out, however, that clinical experience indicates that the concentrated preparations appearing in Table 57 are certainly not less effective than crude liver extract or whole liver, and indeed the use of these preparations has allowed for more complete arrest of neural lesions than is obtainable with less concentrated products. The Advisory Board also refuses to assign a unitage rating to mixtures of liver extract with other substances. It will, however, assign unitage separately to liver and stomach in mixtures containing only these two substances when the potency of the *final* mixture has been assayed by appropriate clinical tests.

Many commercial products of antianemic substances now conform to the U.S.P. system of unitage and assay, and are acceptable to the Advisory Board. In assigning unitage to commercial liver extracts and other antianemia preparations, the Advisory Board (1940) considers the following points in addition to other data from therapeutic tests: the character and degree of the reticulocyte response, the rate of increase of the red blood cells, the efficiency of the method of manufacture in preserving potency, clinical factors modifying the hematological response, and the initial level of the erythrocyte count in relation to the peak reticulocyte response obtained. The prescribing of liver and stomach in terms of U.S.P. units instead of grams and cc's is to be preferred. Some antianemic products of value, however, have not as yet been submitted to the Advisory Board. Consequently, both units and grams or cc's are at present employed in the calculation of dosage, depending upon the preparation selected.

Preparations listed in the N.N.R. conform to the standards of the Council on Pharmacy and Chemistry, as outlined in the N.N.R. The Council has described a rigid method of clinical assay with which all antianemic products intended for inclusion in N.N.R. must conform. This assay is based on standard reticulocyte rises in pernicious anemia patients. The minimal reticulocyte rise allowable varies inversely with the original red blood cell level of the patient used for assay. In the following table are given the standard peak reticulocyte responses at different initial erythrocyte levels as required by the Council in comparison with those suggested by the U.S.P. Advisory Board. However, the U.S.P. standards will become the official figures of the Council at such time as the Council-accepted preparations have been assigned unitages under the U.S.P. regulations.

INITIAL RED BLOOD CELL COUNT	MINIMUM ACCEPTABLE RETICULOCYTE RESPONSE, N.N.R.	RETICULOCYTE RESPONSE SUGGESTED BY U.S.P. ADVISORY BOARD
million per cubic mm	*per cent*	*per cent*
1.0	30	41.8
1.5	18	28.4
2.0	12	18.6
2.5	7	11.1
3.0	4	5.1

The products accepted for inclusion in N.N.R. must be labeled as to the amount of contained material which will produce this standard rise of reticulocytes when assayed in the prescribed manner. In using a Council-approved preparation, therefore, the physician follows the dosage system advised on the package with such changes as the condition and response of his patient require.

Dosage. In this discussion, doses will be given in terms of U.S.P. units; reference to Table 57, however will indicate the number of grams or cc's required in terms of specific preparations. The amount of antianemic material which is necessary to cause a satisfactory hemopoietic response in pernicious anemia varies from patient to patient, but depends mainly upon two factors, the severity of the anemia and the nature and extent of neurological complications. For the average patient in relapse, 15 units may be injected daily for three to four days. Then 15 units may be given two or three times weekly until the reticulocytes have returned to normal and the erythrocytes are on the rise. Fifteen units once or twice weekly may then be injected until the blood is normal. If the patient is first seen when the blood values are relatively high (red blood cell count of three million), the weekly injection of 15 units often suffices to reestablish normal blood levels. The maintenance dose must be found by trial and error but averages approximately 15 units injected every two to three weeks. When oral therapy is employed, daily doses of antianemic material must be administered.

Whether the time interval between parenteral injections of liver extract can be lengthened by increasing to massive doses the amount of potent liver extract injected is a matter of considerable importance to the patient from the standpoint of convenience. In a study of the duration of remission in pernicious anemia after massive doses of liver extract (160 units intramuscularly during a period of one week), Strauss and Pohle (1940) demonstrated that even patients who require relatively little liver extract to maintain a normal blood level (10 units every four weeks) may relapse in as short a time as two months after the massive dose of liver. These investigators concluded that the interval between injections should not be greater than four weeks and that shorter intervals are frequently advantageous.

Patients who have *neurological complications* of pernicious anemia require larger doses of antianemic substance. They must be treated vigorously and the progress of the lesions must be arrested at all cost. It is best, therefore, to give such patients parenteral therapy, and, if the symptoms progress, to increase the amount of liver extract to two or even three times that needed to keep the blood picture normal. Such generous parenteral therapy may turn failure into success. There is abundant evidence that neural damage can be completely arrested, and that considerable improvement may occur if proper therapy is instituted and persistently maintained for many months. Strauss and coworkers (1940) observed 85 cases for seven years. Adequate liver therapy gave excellent results and in no instance did any objective neurological sign become more marked during the period of observation, nor did any abnormal sign, not previously present, appear. There is no standard amount of liver extract which can be prescribed, and the patient's progress is the ultimate guide to dosage. The important point constantly to keep in mind is that the dose needed to maintain a complete hematological remission may be entirely inadequate to prevent neurological regression. It is claimed that unless the mean corpuscular volume of erythrocytes has returned to normal the patient is not protected from further damage to the nervous system. The red blood cell count should be kept above 4,500,000 per cubic mm and the color index below 1.0. Only close and frequent examination of the patient's blood and physical signs can be relied upon to show whether or not medication is adequate.

Patients refractory to therapy require persistent treatment with large doses of parenteral liver extract. Infection is a common cause of refractoriness, as is also myxedema, chronic arthritis and acromegaly. Elderly patients with arteriosclerotic bone marrow often require unusually large doses, and this is also true of women with pernicious anemia of pregnancy. In the last-mentioned disease, the gastric deficiency is temporary, and therapy may be discontinued when pregnancy has terminated. If in spite of large amounts of liver extract the patient fails to respond, one is justified in questioning the potency of the material or the correctness of the diagnosis.

In *summary,* it may be said that the amount of liver extract needed varies with each patient, and that enough should be given to cause a sustained clinical and hematological remission, and to prevent or check nervous system involvement. Only parenteral therapy can be relied upon for satisfactory results in critically ill patients in relapse or those with advanced neurological changes. Whether other patients should receive oral or parenteral preparations depends on factors of cost, personal preference and the results obtained. Medication must be continued without interruption for life. The minimal maintenance dose varies with each patient, and attempts to find this dose should be made cautiously and not

COUNCIL-ACCEPTED ANTIANEMIC PRODUCTS FOR USE IN PERNICIOUS ANEMIA

Class of Preparation	Trade Name of Product	Distributor	Dosage Recommended by Distributor		U.S.P. Unitage *
			Relapse	Maintenance	
Powdered Liver Extract for Oral Administration	Autolyzed Liver Concentrate	Squibb & Sons	34.4 to 44.5 grams (6 to 8 teaspoonfuls) daily for 10 days	17.2 to 22.3 grams (3 to 4 teaspoonfuls) daily	
	Liver Extract	Armour and Co.	14 grams (3 vials or teaspoonfuls) daily	Not stated	4.5 grams = 1 oral unit
	Liver Extract	Eli Lilly & Co.	12.6 to 25.2 grams (3 to 6 vials or teaspoonfuls) daily	Not stated	12.6 grams = 1 oral unit
	Liver Extract	Parke, Davis & Co.	12 to 21 grams (4 to 6 vials) daily	6 to 12 grams (2 to 4 vials) daily	24.0 grams = 1 oral unit
	Liver Extract	Abbott	25.0 grams (50 capsules) daily	Adjusted according to patient's need	25.0 grams = 1 oral unit
Solution of Liver Extract for Oral Administration	Solution Liver Extract	Armour and Co.	45 cc daily in divided doses	45 cc or less daily in divided doses	45 cc = 1 oral unit
	Solution Liver Extract (Oral)	Lederle Laboratories Inc.	60 cc daily	20 cc or more daily	60 cc = 1 oral unit
	Solution Liver Extract	Valentine Co., Inc.	90 cc daily in divided doses	30 cc or more daily	45 cc = 1 oral unit
Solutions of Liver Extract for Parenteral Administration	Three cc Concentrated Solution Liver Extract Parenteral	Lederle Laboratories Inc.	3 cc injected intramusc. daily for 3 or 4 consecutive days	3 cc injected intramusc. weekly	0.3 cc = 1 unit
	One cc Concentrated Solution Liver Extract Parenteral	Lederle Laboratories Inc.	1 cc injected intramusc. daily for 3 or 4 consecutive days	1 cc injected intramusc. once every two weeks	0.06 cc = 1 unit
	Liver Extract (Intramuscular)	Parke, Davis & Co.	2 cc injected intramusc. daily	2 cc injected every 2 or 3 days	2.0 cc = 1 unit
	Ampoules Solution Liver Extract, 1 U.S.P. unit per cc	Eli Lilly & Co.	2 cc injected intramusc. each day	Adjusted according to patient's needs	1.0 cc = 1 unit
	Ampoules Solution Liver Extract, 15 U.S.P. units per cc	Eli Lilly & Co.	2 cc injected intramusc., or 1 cc on two successive days; then 1 cc weekly	1 cc injected intramusc. every 15 days	0.067 cc = 1 unit (15 units per cc)
	Ampoules Solution Liver Extract, 2 U.S.P. units per cc	Eli Lilly & Co.	3 cc injected intramusc. daily for 3 successive days; then 3 cc weekly	Adjusted according to patient's need	0.5 cc = 1 unit
	Liver Extract, U.S.P. 5 units per cc	Abbott	0.5 to 1.0 cc injected intramusc. daily	Adjusted according to patient's need	0.2 cc = 1 unit
	Liver Extract, U.S.P. 10 units per cc	Abbott	0.25 to 0.5 cc injected intramusc. daily	Adjusted according to patient's need	0.1 cc = 1 unit
Desiccated Stomach	Ventriculin	Parke, Davis & Co.	20 to 30 grams by mouth daily	10 grams by mouth daily	
Liver-Stomach Concentrates	Extralin	Eli Lilly & Co.	6 grams (12 pulvules)	4.5 grams (9 pulvules)	

until the patient has been in complete remission for at least one year. The red blood cell level should be kept, if possible, approximately at five million per cubic mm. If the erythrocytes remain stationary near four million per cubic mm, the use of larger doses of liver extract may cause a rise to a more normal value.

The Clinical Use of Antianemic Substances

Preparations. 1. *Fresh Liver Orally.* This therapy was introduced by Minot and Murphy. About 300 to 500 grams of liver must be eaten daily to induce and maintain a remission in patients with uncomplicated pernicious anemia in relapse. The liver must be lightly cooked, and never boiled for long. Calf, cow or pork liver may be used. Several recipes for extracting the juice of liver are available, the active substance being water-soluble. A marked eosinophilia may be noted in patients taking liver orally.

Very few patients today are kept on a liver diet. It is expensive and cannot alone be depended upon in complicated cases requiring large amounts of potent antianemic material. It is difficult for an ill patient with sore tongue and poor appetite to ingest the necessarily large quantities of liver, especially if liver is distasteful to him. In severely ill patients, a satisfactory response is often obtained too slowly. For all these reasons, the advent of liver extracts was most welcome.

2. *Powdered Liver Extract for Oral Administration.* These powders contain the water-soluble fraction G of Cohn, and are official in the U.S.P. They provide a decided advantage over the liver diet and may be taken in cereals, soups, fruit juices, etc. The amount varies with the preparation used and with the severity of the anemia. The available N.N.R. preparations and their unitage and dosage appear in Table 57.

The disadvantages of powdered liver extract taken orally are several. It is an expensive form of therapy. It is difficult for many patients to take large doses due to the unpleasant taste. In severe or complicated cases, liver extract by mouth cannot be depended upon to supply sufficient antianemic substance, to arrest spinal cord lesions or rapidly to restore the patient to a safe blood level. Also, vomiting or diarrhea makes absorption of the drug uncertain.

3. *Solution of Liver Extract for Oral Administration.* This type of preparation, official in the U.S.P., contains the dry liver extract previously described in aqueous or hydroalcoholic solution. The N.N.R. products available appear in Table 57. The solutions are expensive and most patients find the taste disagreeable. This class of liver preparations has the same disadvantages in severely ill patients or complicated cases as those enumerated for the powdered extracts, and is used infrequently today.

4. *Solutions of Liver Extract for Parenteral Injection.* Solutions of liver extract for parenteral injection are official in the U.S.P. Their introduction in 1930 marked a definite advance in the therapy of pernicious anemia. The intramuscular injection of liver extract allows one to give sufficient antianemic substance to cause rapid improvement in those critically ill, and thus blood transfusions are not required as frequently as formerly. Patients refractory for various reasons to oral therapy nearly always respond to adequate parenteral doses of liver extract. The outlook for the patient with neurological complications has improved distinctly since the availability of injectable liver (Strauss and associates, 1940). The expense is also less, especially if the patient administers the injections to himself. For all these reasons, the majority of patients with pernicious anemia today receive parenteral therapy.

There are a large number of preparations available on the market, and those included in the N.N.R. provide the clinician with an adequate range of choice. The Council-accepted products appear in Table 57.

In addition to the advantages of parenteral therapy already mentioned, it should be stated that with the advent of highly concentrated preparations effective in small volume, there is little reason why most patients should not learn to give the injections themselves and thus save the expense and time involved in receiving injections by the physician or attendant. The necessity of using an intramuscular needle and injecting large volumes has acted as a deterrent, but now that doses of one or two cc are adequate, self-injection is quite feasible. The patient with diabetes mellitus is entrusted with the self-administration of a far more potent and dangerous drug in insulin than the pernicious anemia patient has in liver extract. The need for careful medical supervision of the patient, of course, still exists.

Cost of Parenteral Therapy. The monthly cost of maintenance therapy with intramuscular liver preparations for the average patient is between $1.25 and $2.00, at current price levels in the United States. Naturally, this is exclusive of the physician's fee for performing the injection. When dry oral preparations of the antianemic principle are used, however, the monthly expense for maintenance therapy is between $6.00 and $8.00. Cost, therefore, is a major consideration when it is remembered that treatment must continue for the duration of life.

Reactions to Parenteral Liver Extract. These are only seen occasionally, now that extracts are highly purified. Flush and headache suggesting a histamine-like reaction may be noted, and chills and fever sometimes occur. Skin eruptions and urticaria are occasionally observed. Shock-like reactions are rare. In treating the immediate reaction, epinephrine is of great benefit if the symptoms are anaphylactoid in character. In preventing such reactions, two courses are open. Inasmuch as most preparations are made from swine liver, one may shift to beef liver (Campolon-Winthrop) or to horse liver (Chappel). The other method is to desensitize the patient as one would to any allergen.

5. *Stomach Preparations.* Desiccated defatted hog stomach is an official U.S.P. preparation. The only product generally available in this country is *Ventriculin* (*N.N.R.*) (Table 57). It is taken orally as a dry granular powder in soup, cereal, fruit juice, etc., and has the same therapeutic effects as liver. The status of desiccated stomach is the same as that of dry liver extract for oral use, but the preparation is less distasteful to some patients. It is quite certain that the effective substance in desiccated stomach is an interaction product formed by the intrinsic factor in the hog's mucosa acting on the extrinsic factor contained in the wall of the stomach.

6. *Liver-Stomach Concentrates.* The only readily available preparation in this category is *Extralin* (*N.N.R.*) (Table 57). It represents a digestion product of three parts by weight of liver extract and one part of finely minced hog's mucosa. Liver is a rich source of the extrinsic factor and its antianemic potency can be increased ten-fold or more by incubation with gastric juice. The interaction which occurs enhances the potency of the final product above that of the substances entering into the combination, an example of true potentiation. The chief advantage of extralin is that it is the most potent antianemic preparation, gram for gram, that can be taken orally. Extralin is a powder and is marketed in capsules.

Responses to Antianemic Therapy. In patients with uncomplicated pernicious anemia to whom adequate doses of liver extract are given, both objective and subjective improvement occur within a few days after therapy is started. Progress continues until all evidence of the disease disappears. Patients with central nervous system involvement require a longer time for improvement, but progression of the lesions can be arrested. The soreness and smoothness of the tongue and the gastro-intestinal disturbances disappear, and the symptoms due to the anemia are relieved as the blood picture returns to normal. Strength, mental outlook and appetite all improve and within several weeks the patient is symptomatically cured.

The blood response is naturally the most dramatic part of the recovery and is the best measure of the patient's progress. Reticulocytes begin to appear in the peripheral blood within two to five days and reach their peak levels between the first and second week as a rule. The character of the reticulocyte curve and the height reached depend on the dose of liver extract used, the route of administration, and especially on the severity of the anemia. With optimal doses, the reticulocyte peak is inversely proportional to the initial level of red blood cells. Peaks of from 50 to 70 per cent are not uncommon in patients with erythrocyte counts below one million per cubic mm. Due to the definite relationship which exists between the maximum reticulocytosis and the initial red blood cell level when intramuscular liver therapy is employed, one can calculate the expected peak of reticulocytes by use of the formula devised by Isaacs and Friedman (1938), in which R represents the maximum reticulocyte percentage and E_0 the initial erythrocyte count in millions per cubic mm, as follows:

$$R = \frac{82 - 22E_0}{1 + 0.5E_0}$$

Soon after the reticulocyte curve rises, the erythrocytes start to increase in number and values of 4.5 to 5.0 million per cubic mm are ultimately reached. In severe cases, the red blood cells increase about 0.5 million per cubic mm per week. Charts from which the standard erythrocyte responses to intramuscular liver therapy can be readily ascertained have been presented by Isaacs and his associates (1938). The hemoglobin rises more slowly than do the red blood cells, and as a result the color index decreases toward normal. The size of the red blood cell also decreases. Reticulocytes usually return to pre-injection levels by the end of the third week, and the blood appears normal by the second to fourth month. Ideally, the erythrocytes return to normal levels within eight weeks when intramuscular therapy is used. The main features of the hematological responses to liver extract in a severe case of pernicious anemia are illustrated in Figure 104.

Other Measures Employed in Pernicious Anemia. In addition to specific antianemic therapy, the diet should be adequate in all respects. Iron should supplement the liver preparations only if the color index falls below normal. If the achlorhydria is troublesome and gives rise to gastro-intestinal symptoms, from two to eight cc of *Diluted Hydrochloric Acid,* U.S.P., in half a glass of water may be given with each meal. Transfusion of blood is now required only as an emergency measure in critically anemic patients. The intravenous injection of liver extract is rarely needed and may cause severe reactions; intravenous preparations are not acceptable to the Council.

"Shotgun" Antianemic Mixtures. In spite of the low incidence of pernicious anemia, the number of preparations for the therapy of this disease increases yearly. As Dameshek (1938) has pointed out, pharmaceutical houses take pains in concentrating, refining and advertising their extracts in large part because many physicians use them indiscriminately in any patient with anemia, regardless of the etiology. This practice is not only expensive but actually may not be to the best interest of the patient, as it often obscures the real nature of the disease. Several oral liver extracts contain iron and some mixtures have copper and vitamins thrown in for good measure. Strauss (1936) has so tersely stated the reasons for not using such preparations that he is quoted here in full as follows: " 'Shotgun' therapy is to be deplored for a number of reasons. Most mixtures of

substances fail to contain enough of any one ingredient to give maximal effects. The patient must pay not only for the material he needs but also for nonessentials. Mixed therapy may so cloud the clinical picture that accurate evaluation of subsequent therapeutic needs becomes impossible. Most patients with addisonian pernicious anemia require lifelong treatment whereas the majority of patients with anemia due to iron deficiency, once well, will remain well unless the original cause is re-established. Therefore, if a patient, not definitely known to have pernicious anemia, receives both liver and iron and recovers, no conclusion can be drawn as to which was the effective substance. If both should now be stopped, the patient, should he have pernicious anemia, will sooner or later relapse. In addition he runs the risk that his relapse may be essentially neurological and may advance to the stage of irreparable spinal cord injury before the nature of the condition is recognized. On the other hand, if the anemia is of the

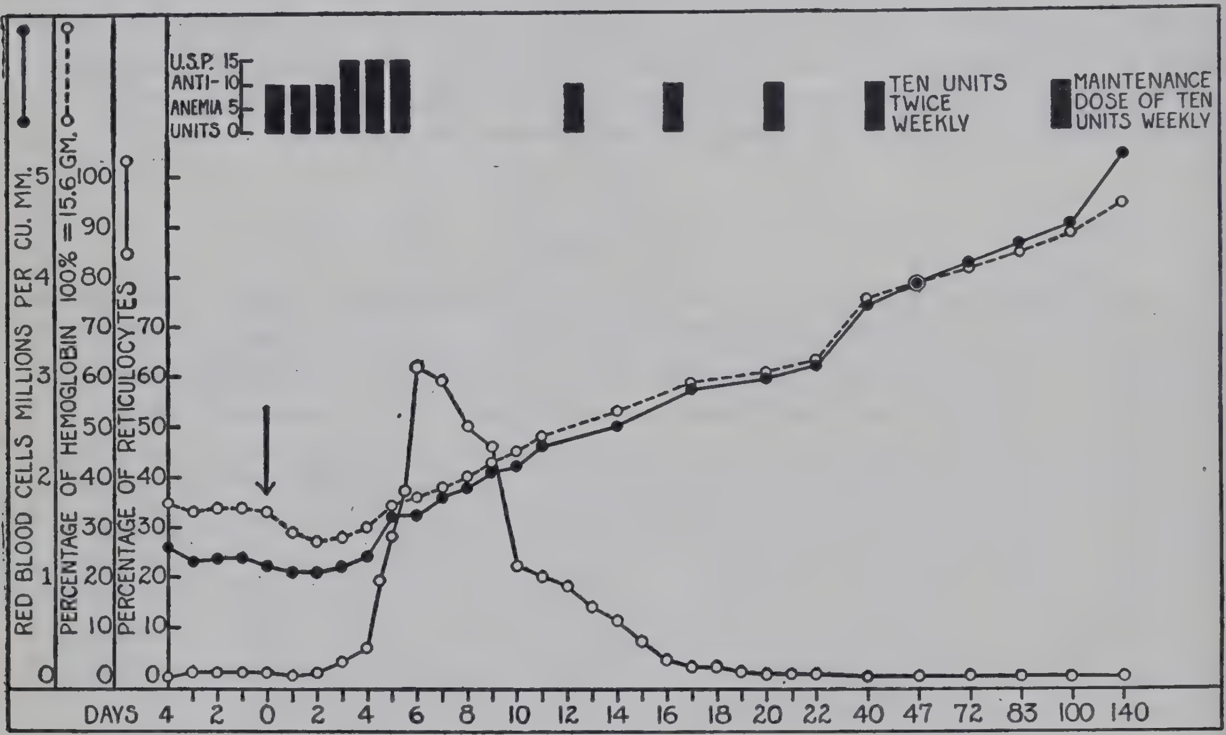

FIGURE 104. *Hemopoietic response of a patient with pernicious anemia to parenteral liver extract.*

White male, aged 58, entered hospital complaining of weakness, loss of appetite and weight, shortness of breath for six months, numbness and tingling of hands and feet. Pertinent *physical findings* were white hair, lemon yellow pallor of skin and conjunctivae, smooth tongue with atrophic edges, gallop rhythm, blowing systolic murmur at apex, absent ankle jerks, weak patellar reflexes, slight impairment of vibration sense, temperature 101.2 F., pulse 100, respirations 24. *Laboratory examinations* revealed no free HCl in gastric contents after histamine and alcohol test meal; R.B.C., 1,100,000; Hb., 4.7 grams%; hematocrit, 14%; mean corpuscular hemoglobin, 42.7; mean corpuscular volume, 127; W.B.C., 1500; differential, polymorphonuclear neutrophils 54%, small lymphocytes 44%, monocytes 2%; marked anisocytosis and poikilocytosis, occasional normoblast, marked macrocytosis; icterus index, 10. *Diagnosis:* Classical addisonian anemia with early posterolateral sclerosis.

Therapy with intramuscular administration of liver extract (started at the arrow) produced the hemopoietic changes indicated in the figure. Note the marked reticulocytosis starting on the fourth day, reaching its peak on the sixth day and declining over a period of 10 days. Observe that the rise in erythrocytes is more rapid than the rise in hemoglobin. The patient's symptoms quickly improved, the mean corpuscular hemoglobin and volume and the character of the blood smear returned to normal by the third week, the subclinical icterus disappeared, and the neurological involvement slowly improved. Note the change in time scale; also the alterations in dosage as the blood values returned toward normal.

iron deficiency type and therapy with both liver and iron is continued, the patient is subjected to the expense and inconvenience of taking an unnecessary liver preparation."

Other Anemias Responding to Liver Extract. In addition to pernicious anemia, there are several closely allied hyperchromic macrocytic anemias which respond in some measure to liver therapy. It is often difficult to determine the exact mechanism of the anemia in these cases; but there is no doubt that some of them at least are on a "liver-deficiency" basis, and thus respond more or less specifically to antianemic preparations. This response is rarely as dramatic as in true addisonian anemia, however, and usually requires the use of much larger doses than necessary in pernicious anemia. Diseases characterized by anemia and responding at times to liver therapy include sprue, pellagra, macrocytic tropical anemia, fish tape-worm anemia, and the anemias somewhat resembling pernicious anemia encountered in certain cases of gastric carcinoma or resection, hepatic cirrhosis and chronic intestinal disease with protracted diarrhea. In the case of pellagra, to mention but one of these syndromes, the disease appears to be due to a deficiency of nicotinic acid and perhaps other constituents of the vitamin B complex. The livers of patients with pellagra contain the antianemic principle, and extracts of them are capable of causing a therapeutic remission in an individual with pernicious anemia (Sydenstricker and coworkers, 1939). The response of pellagrins to liver therapy, therefore, is due to factors in liver extract other than the antianemic substance.

Liver Therapy in Atrophic Gastritis. Liver therapy has been reported to cause improvement in certain cases of atrophic gastritis unassociated with pernicious anemia, posterolateral degeneration of the spinal cord, sprue or pellagra. The improvement is evident symptomatically and by gastroscopic examination (Schindler and coworkers, 1940). The ability to secrete free hydrochloric acid may even return, suggesting that liver therapy causes a true regeneration of functionally active gastric glands. Relapse may occur after liver treatment is withdrawn. Whether liver is specific in certain patients is unknown, particularly because spontaneous remissions are not unusual and because the administration of iron salts occasionally may cause disappearance of atrophic gastritis associated with hypochromic anemia. Nor is it known whether the antianemic principle in liver extract is responsible for the results obtained. Similar symptomatic and gastroscopic improvement in atrophic gastritis has been reported by Schiff and Goodman (1940) after the administration of desiccated hog's stomach (ventriculin).

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CHAPTER 62

MISCELLANEOUS DRUGS AFFECTING THE BLOOD

HEPARIN, NUCLEIC ACID DERIVATIVES AND PHENYLHYDRAZINE

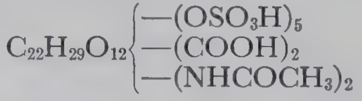
HEPARIN

Historical. It has been known for many years that certain animal tissues contained substances capable of preventing coagulation of the blood. For example, the anticoagulant *hirudin* found in the buccal glandular secretion of leeches has been the object of considerable investigation. In 1916, McLean, working in Howell's laboratory on the thromboplastic behavior of certain phosphatides, isolated an active anticoagulant from liver, to which Howell and Holt (1918) applied the name *heparin* to indicate its origin.

Heparin was available for many years only as a crude extract which was difficult to obtain and which caused numerous toxic side-effects. Therefore physiological and clinical investigations concerning its function, mechanism of action and therapeutic possibilities were hampered. Howell (1925, 1928) then purified heparin to the extent that 1.0 mgm sufficed to prevent 100 cc of shed blood from clotting, showed that the active material was not a phosphatide, and demonstrated its presence in minute quantities in plasma of normal dogs and in larger amounts in the plasma of animals suffering from peptone shock. In 1933, Charles and Scott reported the presence of heparin in various tissues of the body, the lungs being richest. Later, these workers (1936) obtained preparations sufficiently purified for experiments on human beings and thus greatly stimulated research in this field.

Reviews on heparin have been published by Best (1938), Mason (1939) and Jorpes (1939), to which the interested reader is referred for details and extensive bibliographies.

Chemistry and Relation of Chemical Structure to Action. The chemical structure of the active substance in heparin is not known. Jorpes (1935) suggested that heparin was a chondroitinpolysulfuric acid and pointed out that many agents used to prevent blood clotting (pontamin pink, chlorazol sky blue, germanin, etc.) are sulfuric or sulfonic acid derivatives. Bergström (1936) soon demonstrated that synthetic sulfuric acid esters of certain polysaccharides possessed heparin activity. Jorpes and Bergström (1936, 1937, 1939) then found that glucosamine rather than galactosamine was the amino sugar in purified heparin and that heparin therefore was a mucoitin polysulfuric ester, probably containing the monosulfuric and disulfuric as well as the trisulfuric derivatives. Heparin preparations purified by various technics have anticoagulant potencies which increase roughly in proportion to the degree of esterification of mucoitin with sulfuric acid. Charles and Todd (1940), on the basis of their extensive studies on the crystalline barium salt of heparin prepared in various ways, have concluded that heparin is a mucoitin polysulfuric acid in which the basic tetrasaccharide unit (2 mol. *N*-acetylglucosamine and 2 mol. glycuronic acid) contains five sulfuric ester groupings. They have depicted the formula of heparin as follows:



$$C_{22}H_{29}O_{12}\left\{\begin{array}{l}-(OSO_3H)_5\\-(COOH)_2\\-(NHCOCH_3)_2\end{array}\right.$$

This same formula has also been proposed by Reinert and Winterstein (1939).

Jorpes (1938) called attention to the fact that the strong electronegative charge of the heparin polysaccharide may be the basis of the anticoagulant property, because the substance has no reactive groups. Synthetic anticoagulants are also strong acids (such as the azo dyes) or can be produced by the introduction of sulfuric acid groups into polysaccharides. It is interesting to note that polysaccharide sulfuric esters occurring in algae prevent blood from clotting. Basic compounds of high molecular weight are also anticoagulants. Likewise, if the electric charge of heparin is neutralized as with protamine or with the basic dye toluidine blue, heparin is precipitated and its activity inhibited. It is suggested, therefore, that the electric charge of heparin influences the enzymes entering into the clotting mechanism.

Physiological Function. Although there is no proof that heparin serves a physiological function in the body, there is strong indirect evidence that the compound may be important in maintaining the blood in a fluid state. Minute amounts of heparin are detectable in blood. The characteristic metachromatic staining reaction given by the action of toluidine blue on mucoitin- and chondroitinsulfuric acids also occurs when the dye acts on heparin. Likewise, this staining reaction is precisely that given by granules in the mast cells of Ehrlich occurring especially in connective tissue surrounding blood vessels and in organs (lungs and liver) richest in heparin (Holmgren and Wilander, 1937). Indeed, the content of crude heparin, mast cells and ester sulfates of various tissues run parallel to each other. This would indicate that the mast cells produce and secrete heparin, the physiological anticoagulant. Mast cells are especially abundant in the venae cavae, perhaps explaining the delay in postmortem clotting in these veins, and also in the cornea, which may account for the failure of blood to clot after small hemorrhages in this structure. Finally, when an animal is in peptone-induced shock, the clotting time of the blood is prolonged and more heparin can be detected in the blood. Those species which have a paucity of mast cells in their livers, such as rabbits and guinea pigs, do not respond to peptone with significant changes in blood clotting time. On the other hand, a hepatectomized dog in anaphylactic shock shows no increase in clotting time (Waters and coworkers, 1938), and the blood heparin is unchanged, strongly suggesting that the liver is the source of the anticoagulant. There is no evidence that the blood in persons with hemophilia contains an excess of heparin (Evans and Howell, 1931).

Very little is known concerning the metabolism, fate and excretion of heparin in the body. Traces may be recovered from normal urine, and larger amounts after the drug has been injected. The intestine of heparinized animals also yields the anticoagulant substance upon extraction. Heparin is rapidly inactivated by serum at body temperature.

Mechanism of Action. In order to understand the action of heparin in preventing the clotting of blood, the factors operating in the clotting mechanism must be kept in mind. The modern conceptions of this mechanism (*see* reviews by Eagle, 1937, 1939) may be presented briefly and schematically as follows:

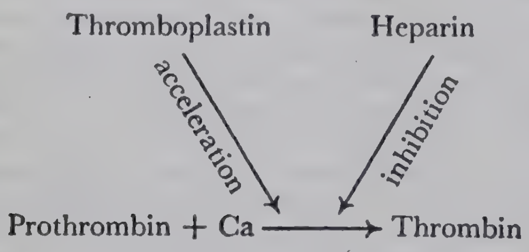
$$\text{Prothrombin} + \text{Thromboplastin} + \text{Calcium} \longrightarrow \text{Thrombin}$$
$$\text{Thrombin} + \text{Fibrinogen} \longrightarrow \text{Fibrin}$$

The proteolytic enzyme thrombin is normally antagonized in the blood by an unidentified antithrombin component of the albumin fraction of the serum proteins, the activity of thrombin thus being held in abeyance and intravascular clotting prevented. Heparin in itself is weakly antithrombic, but when mixed with either serum or plasma, it is many times more antithrombic than either heparin or serum alone. It would thus appear that heparin acts on the thrombin system and not on fibrinogen, combining with the antithrombin component of the serum to form a more active antithrombin.

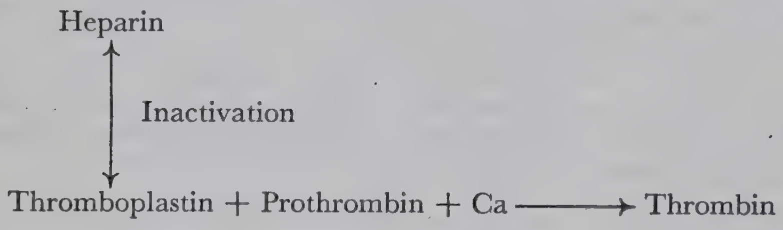
The view was originally advanced by Howell and Holt (1918) that heparin, in addition to being antithrombic, acts as an "anti-prothrombin," *i.e.*, prevents the activation of prothrombin to thrombin. Working in the absence of serum, Quick (1936) could demonstrate no anti-prothrombin activity on the part of heparin. However, in the presence of serum, Brinkhous and coworkers (1939) showed that heparin definitely prevented the activation of prothrombin to thrombin. The concentration of active prothrombin in plasma was not diminished by heparinization. One possibility advanced by these investigators was that heparin acted by antagonizing thromboplastin. They also pointed out that both known actions of heparin—the inhibition of thrombin formation (anti-prothrombin action) and the inhibition of the coagulant action of formed thrombin (antithrombin action)—are seen only when plasma is present. The identity of the plasma component necessary for the activation of heparin is unknown, although it appears to reside in the most soluble fraction of the serum albumin (Quick, 1938; Ziff and Chargaff, 1940).

Heparin could antagonize thromboplastin by three possible mechanisms, as pointed out by Eagle (1939): (1) Heparin and thromboplastin might be functionally antagonistic—one inhibiting and the other accelerating the conversion of prothrombin to thrombin. (2) Heparin may combine with and inactivate thromboplastin. (3) Heparin, combined with and inactivating prothrombin, may be released from such combination by reacting with thromboplastin, thus liberating reactive prothrombin. These possibilities may be diagramed as follows (Eagle):

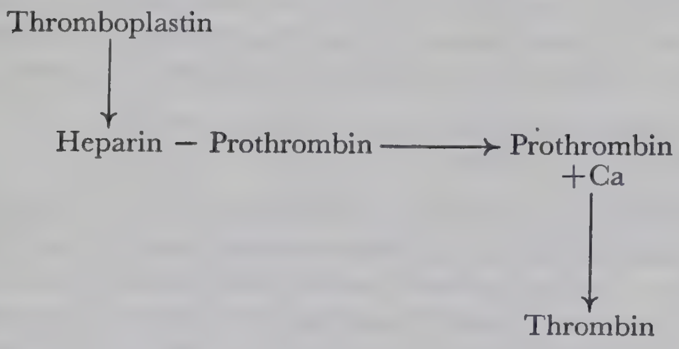
(1)


Thromboplastin
Heparin
acceleration
inhibition
Prothrombin + Ca
Thrombin

(2)


Heparin
Inactivation
Thromboplastin + Prothrombin + Ca
Thrombin

(3)


Thromboplastin
Heparin — Prothrombin
Prothrombin
+Ca
Thrombin

Preparations and Unitage. Preparations of heparin sufficiently purified to use in man have been made available only within recent years. The commercial products generally are prepared by the purification methods outlined by Jorpes and by Charles and Scott (1936, 1940). Preparations of high purity and potency are obtainable from the Connaught Laboratories,* Toronto, and from Hoffmann-La Roche, Inc. The drug may be sterilized by boiling, or by autoclaving at 110 C for not over 30 minutes. Bacterial filters cannot be employed. Sterile solutions of heparin in ampules keep indefinitely.

* "Solution of Heparin" is supplied by the Connaught Laboratories in ampules containing 100 mgm of heparin (10,000 units) in 10 cc of sodium chloride solution. Before use, this solution is usually diluted 50 to 100 times to form a "two" or "one" per cent solution.

The unit of potency of heparin has been variously defined and has undergone numerous changes parallel with the increased activity of the more purified fractions of heparin. The original Howell unit represented the amount of heparin activity which prevented the clotting of one cc of cold cat's blood for 24 hours. A *unit* is at present defined by the Toronto workers as the activity represented by 0.01 mgm of the purest heparin, that is, of a crystalline barium salt of heparin set aside for this purpose at the Connaught Laboratories in Toronto (Murray and Best, 1938). This unit is about five times as large as the Howell unit, and the purest heparin therefore contains 500 Howell cat units per mgm.

Clinical Results and Uses. Heparin may have a number of useful laboratory and therapeutic applications in medicine and surgery. Further experience and the accumulation of more data are necessary before the exact value of heparin can be stated. It must be emphasized that the reported uses of the drug are still in the experimental stage.

Laboratory Uses. Heparin prevents the coagulation of blood without effects which interfere with the usual chemical or cellular examinations. White blood cell counts must be done without much delay in order to avoid agglutination. Osmotic equilibria are not altered and therefore hematocrit determinations may be accurately made. Heparinized blood, however, increases resistance of the erythrocytes to hypotonic salt solutions in fragility tests, alters the sedimentation rate and affects serological reactions involving complement, which is inhibited by heparin.

Experimental Uses. Highly purified heparin may be injected into laboratory animals without untoward or toxic effects. Subcutaneous injections cause only brief anticoagulant action but a continuous intravenous drip containing heparin has proved satisfactory for maintaining effects for hours and days. Dogs, for example, require 25 units (0.25 mgm) per kg of body weight per hour by this route. Anesthesia prolongs and intensifies the anticlotting effects of a given dose of heparin administered subcutaneously. This route, as a rule, is unsatisfactory unless the benzidine salt of heparin is employed, in which case absorption is slow and continuous and the actions of a large dose may be prolonged for forty hours or longer. There is no "negative" phase in the clotting time when the effect of heparin administered to an animal or patient wears off, and the blood does not become hypercoagulable.

Studies in experimental thrombosis have been greatly facilitated by the use of heparin. The drug prevents the thrombotic action of injected thromboplastic substances in animals, and inhibits extracorporeal blood clotting in tubes and arteriovenous shunts. Both *in vitro* and *in vivo,* heparin prevents the accumulation of white thrombi (leukocytes and platelets) (Best, Cowan and MacLean, 1937). Thrombosis due to chemical and mechanical injuries to veins can also be obviated by prior heparinization of the blood (Murray and coworkers, 1937; Solandt and Best, 1938). The percentage of success in arterial anastomoses and cross-suturings of blood vessels is increased by heparinization of animals, and transplantation of organs has been greatly facilitated (Murray and Best, 1938).

In *experimental pleurisy* due to chemical injury, the injection of heparin prevents the appearance of fibrin in the pleural exudate and the subsequent formation of adhesions (Widström and Wilander, 1936). Similarly, heparin prevents *peritoneal adhesions* following mechanical trauma or bacterial contamination (Lehman and Boys, 1940). Experiments involving *cross-circulation exchange transfusion,* whereby the blood of a normal donor clears the blood of a recipient with renal insufficiency of metabolic end-products, have been greatly facilitated (Thalhimer, Solandt and Best, 1938). The application of this technic of reciprocal blood transfusion in man has been reported by Duncan and coworkers (1940).

Therapeutic Uses. Heparin is inactive orally, and not entirely satisfactory when administered subcutaneously in man. Pure preparations of heparin are now non-toxic for man and can be injected intravenously in large doses without untoward effects or changes in respiration, blood pressure, temperature, blood chemistry or formed elements of the blood. A single injection of 60 mgm elevates the coagulation time (after a latent period of 10 minutes) to 30 minutes from a normal of five to seven minutes. The effect wears off quickly, usually within three hours. Smaller doses result in proportionate changes, and multiple injections prolong the effect. Best and his associates prefer to maintain heparinization by a continuous intravenous drip which allows the coagulation time to be set at any desired level for any desired period of time, even up to several weeks (Murray and Best, 1938). The infusion of heparin is adjusted as determined by repeated observation of the coagulation time. A solution containing 10 mgm (1000 units) of heparin per 100 cc of 0.9 per cent sodium chloride is given at the rate of one to two cc per minute, the rate being changed as needed. This allows a two to four-fold increase in coagulation time. No cumulative action is noted and the drug disappears from the blood in 20 to 140 minutes after medication ceases.

Heparin has been used successfully for aiding *blood transfusions,* either by substituting for citrate, by application in solution to syringes, tubing, etc., or by heparinization of the donor. The details and advantages of this use of heparin may be found in the reports of Sköld (1936), Hedenius (1936), Knoll and Schürch (1938), Sappington (1939) and others. When the donor is heparinized, the recipient's coagulation time is elevated for several hours; but with other technics this effect on the recipient is absent, or slight and transient, allowing transfusion immediately before or after surgical operations.

Heparin has been employed with promising results in the attempt to prevent *thrombosis,* especially of postoperative origin. The clinical reports are limited, and before the true worth of heparin can be stated, more data are needed from hospitals where a fairly constant type of postoperative care and a predictable incidence of thrombosis exist. The drug is used for several days by the intravenous drip method in an attempt to antagonize thromboplastic substances liberated into the blood from traumatized tissues, to limit thrombus formation at cut surfaces of vessels, and to prevent coagulation of stagnated blood. For the details of these procedures, and the doses and precautions employed, the reports of Murray and Best (1938), Murray (1940) and McClure and Lam (1940) may be consulted. Of 315 surgical cases of all kinds treated with heparin at the Toronto General Hospital and reported by Murray and Best (1938), none developed pulmonary embolism or thrombophlebitis although many of the operations were of a nature in which these accidents are rather frequent. The same authors also found heparin of value in patients with *phlebitis, pulmonary embolism,* and *peripheral embolism,* the drug probably acting by preventing recurring thrombosis.

In a continuance of this work, Murray (1940) subsequently reported excellent results with heparin in cases of *arterial suture, venous graft, mesenteric thrombosis, splenectomy, blood transfusion, embolectomy, phlebitis,* and *thrombophlebitis and pulmonary embolism.* In an attempt to prevent pulmonary embolism, the above cited series of cases was extended to 440 patients who were heparinized postoperatively, and no thrombosis or embolism occurred in any patient who was free from it at the beginning of treatment. In those who had thrombosis, there was no extension of the process. In 81 cases of *thrombophlebitis* in which heparin was employed, pulmonary embolism was not observed in a single instance (although the previous incidence of this complication was 15 per cent in 300 cases). In 29 patients with *massive pulmonary embolism* treated with heparin, none died of the embolism, and with but one unproved exception none of the patients had further emboli.

Reports of the usefulness of heparin in resection of the large bowel for *mesenteric thrombosis* (Murray and McKenzie, 1939), in *thrombosis of the central vein of the retina* (Holmin and Ploman, 1938; Boström and William-Ollson, 1938), and in *coronary thrombosis* have appeared, and Magnusson (1938) records its employment in *thrombosis of the posterior-inferior cerebellar artery.* Perhaps the benefit is based on the prevention of further coagulation of blood or extension of the thrombus.

In a report on the successful use of general heparinization in the therapy of *postoperative pulmonary embolism,* and *peripheral arterial embolism and thrombosis,* McClure and Lam (1940) point out that some patients require such a large dose of heparin (2000 units per hour) in order to maintain an optimum clotting time that considerable blood dilution and edema may appear from the large volume of sodium chloride solution employed (200 cc per hour). This complication is particularly important in the presence of cardiac or renal insufficiency. If it is necessary to restrict the amount of fluid administered, the heparin may be given in a more concentrated form (2000 units or more per 100 cc). Indeed, in one case, McClure and Lam repeatedly injected the undiluted solution (10,000 units per 10 cc) without untoward effects.

In the treatment of *subacute bacterial endocarditis* due to *Streptococcus viridans,* an almost invariably fatal disease, heparin has had a preliminary trial in an attempt to prevent further thrombotic deposition of fibrin and platelets on the surfaces of the valves of the heart. Such therapy, if successful, helps to restrict the nidus for bacterial growth, to prevent embolism and to check the growth of vegetations. Heparin combined with sulfapyridine or other sulfonamide drugs may offer some promise in an otherwise hopeless disease (Kelson and White, 1939; Friedman, Hamburger and Katz, 1939).

NUCLEIC ACID DERIVATIVES

A number of nucleic acid derivatives are capable of producing a neutrophilic leukocytosis when injected into animals and man. Some of these have been found efficacious in the treatment of agranulocytic angina, especially pentose nucleotide and adenine sulfate.

PENTOSE NUCLEOTIDE

History. It has been known for many years that nucleic acids and their hydrolytic products have an influence on the total white blood cell count of animals. As early as 1897, Ames observed that nucleinic acid produced leukocytosis and Ewald in 1913 found that yeast, nucleic acids from thymus, xanthine and guanine, but not uric acid, produced rises in leukocyte values in dogs. Sodium nucleinate was shown by Neymann (1917) to cause leukocytosis in man. The extensive studies of Doan, Zerfas, Warren and Ames (1928) demonstrated that leukocytosis was preceded by transient leukopenia and that sodium nucleinate from yeast, yeast nucleotides, adenylic acid and guanylic acid all produced the same hemopoietic response. In experiments on rabbits Reznikoff (1929) noted that the purine bases, adenine sulfate and guanine hydrochloride, produced leukopenia followed by leukocytosis.

In 1930, Reznikoff reported that the intravenous injection of adenine and guanine in patients with agranulocytosis caused an increase in polymorphonuclear neutrophils. In 1931, Jackson and his associates obtained similar clinical results by the use of crude nucleotides obtained from an alkaline hydrolysis of yeast.

Chemistry and Preparations. Pentose nucleotide is derived from nucleic acid of yeast. Nucleic acids are of two origins, plant and animal, yeast nucleic acid and thymonucleic acid being the best examples, respectively. The hydrolytic products of nucleic acids are manifold and all have been chemically identified, but those of plant origin differ slightly from those of animal origin. Both types of nucleic acids yield two purine bases, two pyrimidine bases, phosphoric acid and sugar. Plant nucleic acids consist of the purine bases adenine and guanine, the pyrimidine bases cytosine and uracil, and the pentose sugar d-ribose. The bases when united to a sugar form mononucleosides, and if phosphoric acid is linked to the mononucleosides, mononucleotides are obtained. The latter are called pentose nucleotides because the sugar has five carbon atoms.

The commercially available *pentose nucleotide* contains the sodium salts of four nucleotides from the ribonucleic acid of yeast. The Council-accepted preparation is *Pentnucleotide* (N.N.R.), which is marketed in sterile aqueous solution in 10 cc vials, each vial containing 0.7 gram of the drug.

Pharmacological Actions. Nucleotides and their hydrolytic products exhibit a large number of unrelated pharmacodynamic properties in the mammalian organism. Inasmuch as these are not made use of therapeutically and are seen only with relatively large doses in experimental animals, they are mentioned briefly. The cardiac rate is slowed, and conduction tissue and specialized nodes of the heart are usually depressed. The blood pressure is lowered, in large part through direct peripheral vasodilatation, particularly by the adenyl series. The intestinal musculature is inhibited but the uterine muscle is stimulated. For the details of these actions, and for the possible relations of the compounds to reactive hyperemia, vasodilatation accompanying muscular activity, and the response of tissue to injury, the interested reader is referred to the review by Drury (1936).

The only important therapeutic action of the pentose nucleotides is confined to *white blood cell precursors* in the bone marrow, the growth of which is stimulated, especially if it has been depressed. The increase in total leukocyte count is mainly due to a specific action on the polymorphonuclear neutrophils. The exact mechanism of this stimulation is not clearly understood, principally because all the factors controlling the relative constancy of the number of leukocytes and the percentage of each type are not known. There is reason to believe that the normal physiological stimulus for the leukopoietic tissues consists of the nuclear breakdown products released by the constant disintegration of a certain number of the circulating white blood cells. On this basis, the leukocytosis incident to mild doses of benzol and x-ray may perhaps be explained (Doan, 1933). Whether this is true or not, the nucleotides are among the most potent agents available for stimulating production of leukocytes when they are specifically depressed.

Doses and Routes of Administration. The usual dose for patients with agranulocytosis is 10 cc of pentnucleotide twice daily. The solution is injected deep in the gluteal muscles. Therapy is continued for at least five days or until the desired leukocyte response is obtained. In gravely ill patients, it is recommended that 20 cc be injected twice daily for at least four days, then 10 cc twice daily until the leukocyte count has definitely increased. One injection of 10 cc per day is then continued until the count has been normal for at least three days. It must be remembered that the cellular response does not occur immediately and that an increase in leukocytes in the peripheral blood may not be evident until the third to the fifth day (Figure 105).

Untoward Reactions. The side-reactions encountered from the intramuscular injection of pentose nucleotides are not serious, as a rule, and generally no untoward response occurs with the smaller doses. Untoward effects consist of chills, fever, a "tight" sensation in the chest, a feeling of tension and "inner excitement," followed by lethargy, semi-stupor and dullness. The symptoms usually are temporary and disappear within an hour. When intravenous administration is employed, reactions are more frequent and severe and this route should therefore be avoided if possible. Symptoms noted are the sharp onset of dyspnea, precordial distress, bradycardia and sweating, but these too are usually transient. Precordial distress may be relieved by atropine sulfate. If intravenous medication is required for any reason, the drug should be given well diluted with physiological sodium chloride solution, and the injection made slowly and cautiously.

Clinical Uses and Efficacy. Agranulocytosis (agranulocytic angina, malignant neutropenia, granulocytopenia) is a syndrome characterized by a marked decrease in white blood cells due especially to the disappearance of the granulocytes. In true agranulocytic angina, the erythrocytes and platelets remain unaffected. The disease is usually accompanied by fever and ulcerative lesions of mucous membranes, which may become gangrenous. The mucosal lesions are not primary but are the result of the granulocytopenia. The disease is serious and the mortality rate is high. The primary or idiopathic form of agranulocytosis is of unknown etiology, but the secondary type may be due to any one of a number of etiological agents. Important among these causative agents are certain drugs including arsenicals, gold salts, dinitrophenol, benzol, sulfanilamide, and especially aminopyrine. The importance of aminopyrine in the causation of agranulocytosis is discussed under that drug. The pathological physiology underlying the disease is a maturation arrest of the precursors of granulocytes in the bone marrow, which is crowded with primitive cells, for some reason prevented from maturing. This is reflected in the peripheral blood by a paucity or disappearance of granulocytes, the complete absence of which is incompatible with life for more than a few days. Most of the characteristic symptoms of the disease are secondary to the blood disturbance.

Pentnucleotide given to patients with agranulocytosis may cause remarkable improvement. Within 48 hours to four or five days, immature granulocytes and monocytes begin to appear in the peripheral blood and the total leukocyte count rises (Figure 105). Bone marrow puncture reveals improvement even before the peripheral blood picture has altered. The white blood cell count may continue to rise, and values of 15,000 to 20,000 per cubic mm are not unusual within a week or two after the start of therapy. The improvement in the blood picture is reflected in the parallel amelioration of signs and symptoms of the disease.

The *clinical status* of pentnucleotide therapy is indefinite. The pattern of hematological response during recovery from agranulocytosis is not peculiar to patients treated with pentnucleotide, but is purely a physiological one and may occur spontaneously or with other forms of therapy. Some clinicians experienced in its use, however, consider the drug just as specific for the treatment of agranulocytosis as is liver extract for pernicious anemia. Others are less enthusiastic, and poor results from its use have been reported. Jackson and his associates, who first introduced the drug, claim that many of the failures with pentose nucleotide may be attributed to the use of too small a dose, and they recommend 40 cc a day (Jackson, 1935). Due to the fact that the response to the drug is not immediate, treatment should be instituted as early as possible or the patient may not survive sufficiently long to derive benefit from pentose nucleotide.

The latent period between the administration of the drug and evidence of improvement often makes it difficult to determine whether the pentnucleotide was the causative agent in the blood response. There can be little doubt that some of the failures were due to incorrect diagnoses, and that the diseases being treated were aplastic anemias, aleukemic leukemias, or severe leukopenias due to some other cause. On the other hand, some of the successes reported with pentnucleotide may well have been cases of spontaneous recovery. Jackson and Tighe (1939) have analyzed the treatment and mortality in 390 cases of acute agranulocytic angina. They report a mortality rate of 78 per cent in 75 untreated cases, 70 per cent in 43 cases receiving general hospital care without specific therapy, 77 per cent in 130 cases receiving inadequate amounts of any supposedly specific therapy, 62 per cent in 26 cases treated with adequate amounts of liver extract, and 35 per cent in 85 cases treated with pentose nucleotide. The results with pentose nucleotide agree with those reported by Jackson and Parker (1935). The investigators reemphasize the necessity of giving doses of at least 40 cc per day. Inasmuch as the mortality rate from agranulocytosis is high, the use of pentose nucleotide is probably justified despite the lack of adequate proof of a specific curative action of the drug.

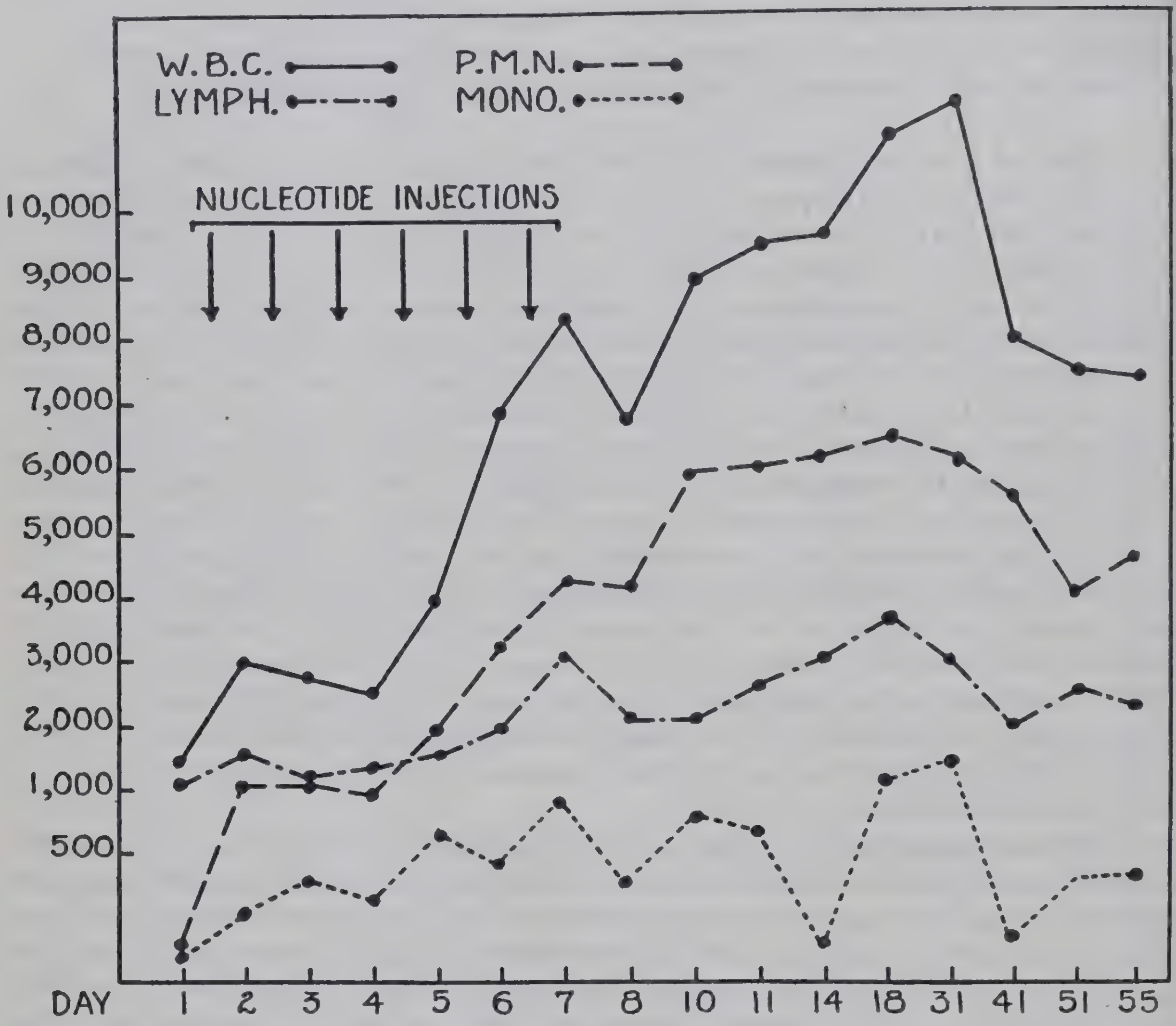


FIGURE 105. *Therapy of malignant neutropenia with pentose nucleotide.*

Female, aged 36, severe malignant neutropenia. W.B.C., 1400, two per cent normal granulocytes. The patient was treated by the daily intramuscular injection of 0.7 gram of pentose nucleotide for six successive days. Slight improvement occurred within 24 hours after the first injection, but a satisfactory gain was not observed until the fourth day. The increase in neutrophilic granulocytes paralleled that of the total white blood cell count. Note change in scales for time and number of white blood cells. (After Doan, 1932. Courtesy of *The Journal of the American Medical Association.*)

ADENINE SULFATE

Reznikoff (1930) was the first to employ the purine bases, guanine and adenine, in the therapy of agranulocytosis, and adenine sulfate has been found to be as effective as pentose nucleotide. Adenine sulfate is not used frequently, however, because it is not so readily obtainable as pentose nucleotide.

Chemistry, Mechanism of Action and Administration. The chemical relationship of adenine to pentose nucleotide has been discussed. Adenine sulfate is the salt of a simple purine base obtained from yeast. It is insoluble except in hot water. The dose usually employed is 1.0 to 2.0 grams. This is given intravenously, dissolved in 30 to 60 cc of 0.9 per cent sodium chloride solution. The solution of adenine sulfate should be freshly made, sterilized by boiling and given while still warm, great care being taken to avoid extravasation. Injections may be repeated two or three times daily, and should be continued for at least three days. The mechanism of action is thought to be identical with that of pentose nucleotide; indeed, the latter may be effective by virtue of its content of purine base. Adenine sulfate is not an official drug and is not included in N.N.R.

Clinical Uses and Reactions. The discussion concerning the clinical use of pentnucleotide applies equally well to adenine sulfate. The drug apparently causes fewer reactions than does pentnucleotide given intravenously, and the claim is made that it acts more rapidly, often within 24 hours, in stimulating the bone marrow. Of 13 patients treated with adenine sulfate by Reznikoff, 10 recovered. Adenine sulfate is preferred to pentnucleotide by some hematologists (Reznikoff 1933; Dameshek, 1933, 1938).

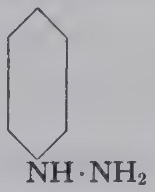
Other Measures for Therapy of Agranulocytosis. If at all possible, the cause of the disease should be removed and suspicious medication stopped. Unfortunately, drug mixtures containing aminopyrine have at times been given for the relief of headache and other symptoms characteristic of the onset of agranulocytic angina. Intelligent nursing care, adequate fluids and nourishment, and full doses of pentnucleotide or adenine sulfate in addition to symptomatic measures should be employed. Injections of liver extract intramuscularly, non-specific proteins, turpentine, and other substances have been tried but there is no evidence that the occasional reported success may not be entirely unrelated to therapy. Small repeated transfusions have a more rational basis, and leukocytic cream —the leukocytes obtained from centrifuging pooled blood of several donors—has also been used intramuscularly. Blood from cases of leukemia has also been employed. X-ray therapy is too dangerous because it is impossible to judge the dose which will stimulate rather than further depress the bone marrow. Drastic local measures for treating the mucosal lesions should be avoided.

Yellow Bone Marrow Concentrate. Sporadic observations have been made on the effect of yellow bone marrow concentrate in the treatment of agranulocytosis. It is claimed that a granulopoietic response is obtained within 48 hours (Marberg and Wiles, 1937, 1938). The clinical evidence for the value of marrow concentrate, however, is meager and its status is doubtful (Council Report, 1939).

PHENYLHYDRAZINE HYDROCHLORIDE

Phenylhydrazine hydrochloride was introduced by Owen in 1924 for the symptomatic treatment of polycythemia rubra vera, a disease characterized by markedly elevated erythrocyte and hemoglobin values. The only other use for the chemical in medicine is as a reagent for identifying urinary sugars by means of the osazone test.

Chemistry and Preparations. Phenylhydrazine base, $C_6H_5NH \cdot NH_2$, is a yellow oily liquid having the following structural formula:



Phenylhydrazine

The hydrochloride of phenylhydrazine is the salt used in therapeutics. It is a buff-colored powder which is very soluble in water; but aqueous solutions darken when left in contact with air. The chemical is not official and is not included in N.N.R.

Pharmacological Actions. The only valuable pharmacological action of phenylhydrazine is on red blood cells. It is usually stated that the chemical destroys erythrocytes by hemolysis, and phenylhydrazine hydrochloride is therefore classed as a hemolytic agent. That this is contrary to fact can readily be ascertained by placing the drug in contact with shed blood at body temperature. Although the chocolate-brown color indicating the formation of methemoglobin appears rapidly, no hemolysis is detectable even after several days. The probable mechanism of action is that the drug readily enters erythrocytes, splits hemoglobin in part to hemin and denatured globin, and the hemin, acting as a catalyst, changes the remaining hemoglobin to methemoglobin and perhaps other unidentified substances. Methemoglobin-containing cells apparently are more vulnerable to physiological stress and to destruction by the reticulo-endothelial system. The result is the disintegration of erythrocytes. The clinical picture resembles a typical hemolytic crisis if the destruction occurs rapidly. The released hemoglobin and cellular products are handled in the usual manner by the body, accounting for the enlarged and tender spleen, and the hyperplasia of the reticulo-endothelial system of the spleen, liver and bone marrow noted after large doses of the drug. The hemoglobin iron liberated by phenylhydrazine is retained in the body and used for hemoglobin regeneration. The pathological changes produced in animals by phenylhydrazine have been studied by several investigators, but the alterations observed are for the most part dependent upon and explained by the primary action of the drug on erythrocytes.

Absorption and Excretion. Absorption of phenylhydrazine hydrochloride occurs readily from the intestinal tract. Excretion of the chemical occurs through the kidney but at a slow rate, allowing for a cumulative toxic action when medication is chronic. The urine of a patient receiving phenylhydrazine may turn a dark color on standing exposed to air.

Dosage and Route of Administration. Phenylhydrazine hydrochloride is always given by mouth, in capsules. The usual dose is 0.2 gram once daily for from three to four days, then 0.1 gram daily until the hemoglobin or erythrocyte level has fallen to the desired extent, which may require several weeks. Maintenance therapy, if employed, is usually at the dose level of 0.1 gram twice weekly, but depends on the hematological response obtained.

Clinical Efficacy, Precautions and Toxicity. The mechanism whereby the physiological values for erythrocytes and hemoglobin are maintained with constancy is still unknown. In untreated cases of polycythemia rubra vera, the red blood cells may rise to from eight million to 14 million per cubic mm. The latter figure is in the uppermost limit theoretically possible, provided the cells retain a normal mean corpuscular volume. The hemoglobin is correspondingly elevated and may range between 18 and 24 grams per 100 cc of blood. The viscosity of the blood is increased five- to eight-fold above normal. The total blood volume may be almost twice the normal in some patients and the total red blood cell mass is thus markedly elevated.

The *etiology* of the disease is not understood. The increase in erythrocytes is not due to increased longevity or decreased destruction of the cells. Most investigators believe that anoxia of the bone marrow may be the cause of erythremia or at least an important factor in its pathogenesis. Reznikoff (1939) has reported that in 16 cases of polycythemia the bone marrow obtained at autopsy or biopsy showed markedly thickened capillary walls and, in most cases, adventitial and subintimal fibrosis of the arteries and arterioles. Control bone marrows did not show these lesions. The cause of the vascular pathology is not known but the observations cited suggest that polycythemia may be due to local anoxia of the bone marrow itself.

Therapy is purely symptomatic and is designed to alleviate the many distressing symptoms and signs which characterize the disease or follow in the wake of the abnormal constitution of the blood. Hemorrhages, thromboses, cyanosis, splenomegaly, hepatomegaly, headache, weakness, vertigo, dyspnea, peptic ulcer, gastro-intestinal disturbances, pain in the extremities, hypertension, etc., all yield in some degree as the blood values are brought to a more normal level by drugs or other measures.

In polycythemic patients, phenylhydrazine hydrochloride in proper doses causes a reduction in hemoglobin and red blood corpuscles. Intermittent therapy may have to be continued over a period of years because the disease is chronic and incurable. Some patients may enter a remission and be able to discontinue the drug entirely after two to four years of treatment, but it is not clear whether remissions are induced by drugs. In an interesting case treated longer than seven years, Stealy (1932) obtained good results by giving the drug (0.1 gram daily) in courses lasting three weeks, with rest periods of six weeks between courses.

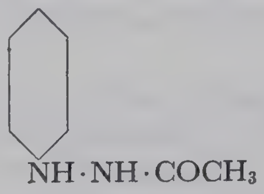
Phenylhydrazine hydrochloride is a drug which commands respect. It can produce harmful effects, and necessitates close observation of the patient and careful regulation of the dose in order to obtain beneficial results. The red and white blood cell counts and the hemoglobin value must be carefully followed. As the hemoglobin value approaches 100 per cent, the drug should be stopped because it continues to act after medication ceases. The leukocyte count is important because it is generally true that a sudden increase in the white blood cell count may herald the onset of acute toxicity from phenylhydrazine. The elevation of white blood cells, which may occasionally reach 50,000 or more per cubic mm, may be due to the destruction of erythrocytes rather than to a toxic effect of the drug or a direct stimulation of the leukopoietic elements of the bone marrow. It is of interest to note in passing that in some cases of polycythemia, the disease apparently terminates in a true leukemia. Some authorities believe that polycythemia and leukemia may coexist (erythroleukemia).

The liver and kidneys are considered to be the organs where damage may occur either from the drug itself or from the rapid destruction of erythrocytes. Renal and hepatic functions should therefore be observed during phenylhydrazine medication. Rapid blood destruction may be fatal due to renal injury and anuria. The drug should be used only with considerable caution in aged or arteriosclerotic patients, and perhaps only ambulatory individuals should receive it. Advanced bed-ridden patients or those with visceral damage or vascular accidents such as thrombosis should not be given phenylhydrazine. Jaundice, anorexia, nausea and vomiting, dermatitis and an increased tendency to thrombosis are among the main toxic symptoms of overdosage.

ACETYLPHENYLHYDRAZINE

Acetylphenylhydrazine was introduced as a drug nearly fifty years ago under the name of *pyrodin*. It was first used as an antipyretic, but the doses required were found to result in toxic reactions. Stone and coworkers reintroduced the drug in 1933 for the symptomatic therapy of polycythemia.

Chemistry and Preparations. Acetylphenylhydrazine is a white powder, slightly soluble in water. On standing in the air, its solutions darken. It has the following structural formula:



Acetylphenylhydrazine

The drug is not official and is not included in the N.N.R.

Dose and Route of Administration. Like phenylhydrazine hydrochloride, acetylphenylhydrazine is given orally in capsules. The dose is 0.1 gram daily for from seven to 10 days, followed by a rest period of two weeks. The temporary discontinuance of medication is observed regardless of the results obtained in order to prevent cumulative toxic effects. If maintenance therapy is needed, 0.1 gram given every five to seven days usually suffices, but the dose must be adjusted to individual requirements.

Clinical Uses. The precautions outlined for phenylhydrazine also apply to acetylphenylhydrazine. The drug is considered to cause fewer gastro-intestinal upsets than the parent substance, to allow a somewhat easier regulation of dose, and perhaps to have a wider margin of safety (McAlpin and Smith, 1938). Although acetylphenylhydrazine produces methemoglobin and causes destruction of erythrocytes indirectly in this manner rather than by a direct hemolytic action, there is some evidence that its mechanism of methemoglobin production differs from that of phenylhydrazine.

Other Measures Used in Polycythemia. In addition to the two drugs described, other measures are employed in polycythemia. *Fowler's solution* (solution of potassium arsenite) in increasing doses reaching 1.2 cc three times daily may be of benefit (Forkner and associates, 1933). The method of administering arsenic is similar to that employed in leukemia (page 745). Benzol is too toxic and its use in therapy is obsolete. Iron salts, liver extract, and repeated gastric lavage have been tried without rational basis or success. *Roentgen ray* treatment, especially "spray radiation," may yield excellent results in some cases.

The oldest treatment for polycythemia and one which apparently is safe and effective is *venesection*. The removal of blood should be repeated until an iron-deficiency state is produced (Stephens and Kaltreider, 1937). Dameshek (1938) reports good results in 10 consecutive patients by removing 500 cc of blood twice weekly for three to four weeks and by the simultaneous use of an iron-poor diet. The objective is to obtain a blood level with a hemoglobin value of 75 to 85 per cent and an erythrocyte count of five to seven million per cubic mm. Symptoms may clear completely and additional therapy is usually not required for six to nine months, at which time another small series of blood-lettings may be necessary. The blood may be used for transfusion purposes. Venesection does not affect the bone marrow deleteriously, neither stimulating nor depressing hemopoiesis.

As Reznikoff (1939) has emphasized, the patient rather than the blood must be treated. Emotional factors are important because the polycythemic individual is usually nervous and irritable. The diet should be bland and non-irritating in order to prevent trauma to the gastro-intestinal mucosa. Alcohol and hot liquids should also be avoided. The patient should remain ambulatory as much as possible because bed-rest may favor the development of thromboses.

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SECTION XV

DRUGS OF ENDOCRINE ORIGIN

Preparations of endocrine glands in the form of crude extracts or purified synthetic active principles may be classified from a pharmacological viewpoint as drugs of animal origin. Whereas most drugs are substances foreign to the body, the hormones are normally present and active in tissues where they have a physiological function. For this reason there is some tendency to place hormones in a different category from drugs. There is no valid reason for this, however, and indeed the older endocrine preparations have unobtrusively broken down this arbitrary distinction. For example, epinephrine is much more frequently viewed as a powerful sympathomimetic drug than as the hormone of the adrenal medulla.

The fact that the drugs of endocrine origin do have a physiological function has aided considerably in the elucidation of their mechanisms of action. A drug foreign to the body can only be studied with respect to its positive effects after administration. Observations on the response to a deficiency or an excess of a hormone can be made both in the clinic and in the laboratory. With this dual investigative method, much has been learned concerning the mechanisms of action of the hormones. Despite the extensive physiological and pharmacological evidence available, the endocrine preparations are probably more often misused in therapy than any other group of drugs. Extravagant claims are often made for their efficacy, and they are widely employed in conditions entirely unrelated to hormonal deficiency. Routes of administration are frequently used which preclude the possibility of obtaining pharmacodynamic action. Rational therapeutic employment of drugs of endocrine origin clearly depends on a thorough knowledge of their chemistry, and of their physiological and pharmacological actions.

CHAPTER 63

THYROID

Historical. The thyroid gland was first described by Wharton in 1656. Harington (1935) reviewed the many older and often amusing opinions concerning the function of this gland. Thus Wharton thought that the viscous fluid within the follicles lubricated the trachea. He also believed that the gland was larger in women to serve a cosmetic function in giving grace to the contour of the neck. Later observers, influenced by the liberal blood supply of the gland, believed that it functioned as a vascular shunt for the brain. With this latter function in mind, the larger size of the gland in women was thought by Rush (1820) to be "necessary to guard the female system from the influence of the more numerous causes of irritation and vexation of mind to which they are exposed than the male sex." However, Hofrichter (1820) ingeniously opposed this theory by pointing out that, "If it were indeed true that the thyroid contains more blood at some times than at others, this effect would be visible to the naked eye; in this case women would certainly have long ceased to go about with bare necks, for husbands would have learned to recognize the swelling of this gland as a danger signal of threatening trouble from their better halves."

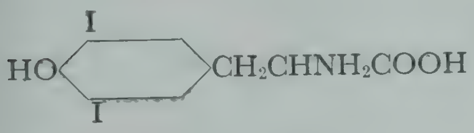
Numerous other theories of thyroid function were advanced, based upon little or no experimental evidence. The belief ultimately became prevalent that the gland served no important physiological rôle. It was not until 1874 that Gull first associated atrophy of the gland with the symptoms now known to be characteristic of thyroid deficiency. Hypofunction of the thyroid in adults is still known as *Gull's disease.* The term *myxedema* was applied to the clinical syndrome by Ord (1878) in the belief that the characteristic thickening of the subcutaneous tissues was due to an excess mucus formation.

Extirpation experiments to elucidate the function of the thyroid were at first misinterpreted because of the simultaneous removal of the parathyroids. However, the pioneer research on the latter organs by Gley (1891) allowed the functional differentiation of these two endocrines. Murray (1891) was the first to treat a case of hypothyroidism. He injected an extract of the thyroid gland and in the following year, Howitz, Mackenzie and Fox independently demonstrated the clinical efficacy of the oral ingestion of thyroid tissue.

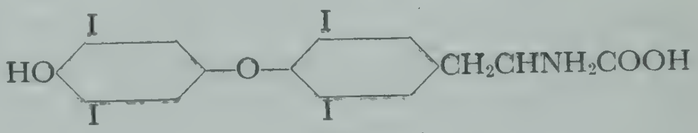
Magnus-Levy in 1895 made the epochal discovery of the effect of the thyroid on metabolic rate. He demonstrated that Gull's disease was characterized by a low basal metabolic rate and that the administration of thyroid to hypothyroid or normal individuals increased the oxygen consumption.

Chemistry. The red-staining colloid material of the thyroid gland is presumably the thyroid hormone. It is an iodine-containing globulin (thyroglobulin) with a molecular weight of 675,000. Intensive investigation of the products of hydrolysis of thyroglobulin resulted in the isolation by Kendall (1915) of a crystalline substance containing 65 per cent iodine which had the same physiological effects as the original protein. This was called *thyroxin,* but the formula was not elucidated until Harington (1926) proved its structure. In the next year, Harington and Barger synthesized thyroxin and thus removed all doubt as to its chemical constitution.

The thyroxin content of thyroglobulin accounts for approximately half of the total iodine. The remainder of the iodine is in the form of diiodotyrosine. The structures of these amino acids are as follows:



Diiodotyrosine



Thyroxin

Thyroxin is optically active. It was formerly thought that the levorotatory form was three times as potent as the dextrorotatory, but now it is believed that the optical activity of thyroxin bears no relationship to physiological activity (Salter, Lerman and Means, 1935).

The physiological activity of the supposed chemical precursors of thyroxin in the body, notably tyrosine and diiodotyrosine, have been investigated in order to determine their relative potency. The metabolic effect in man of diiodotyrosine was found to be only 1/10,000 that of thyroxin (Thompson and associates, 1935). Tyrosine is even less active than diiodotyrosine (Canzanelli and Rapport, 1933).

The fact that half the iodine of the thyroid is in the form of the relatively inactive diiodotyrosine would lead to the belief that, on the basis of the iodine content, thyroglobulin would prove to be only half as active as thyroxin. This concept was supported by the finding that after partial hydrolysis of thyroglobulin it is possible to separate the resulting peptones into two fractions, one containing thyroxin in chemical combination with amino acids (thyroxin peptone), the other diiodotyrosine in essentially the same form (diiodotyrosine peptone). The latter fraction is inactive, whereas the activity of the former is equal to the thyroxin content. Nevertheless, it has been demonstrated by Means, Lerman and Salter (1933) that on the basis of iodine content, the activity of thyroglobulin is as great as either thyroxin peptone or thyroxin itself. Therefore one must conclude that diiodotyrosine in the original molecule is as active as thyroxin despite the fact that when isolated in pure form or in the form of a polypeptide it loses its physiological effects. Barger (1935) postulated that the manner in which this amino acid is linked in the original protein might account for its activity. However, as an alternative hypothesis, Salter and Pearson (1936) demonstrated that diiodotyrosine peptone, a physiologically inactive product, when subjected to enzymatic synthesis with pepsin can be converted into a physiologically active protein containing thyroxin. Salter believes that it is this enzymatic synthesis which accounts for the 100 per cent activity of the iodine-containing amino acids of the thyroglobulin when the latter substance is administered orally.

Thyroglobulin is the only native protein which contains thyroxin and is capable of affecting the metabolic rate by a specific hormonal mechanism. However it is possible to endow nondescript proteins with physiological activity by the simple procedure of treating them with iodine. This was first shown by Abelin and Florin (1933) and the observation has been confirmed by Lerman and Salter (1939). Practically all proteins yield iodized products possessing thyroid activity and Ludwig and von Mutzenbecher (1939) and Harington and Rivers (1939) have isolated thyroxin from iodized casein.

Lerman and Salter (1939) assayed the activity of iodized serum protein on patients with athyreosis. In comparison with thyroglobulin the iodized serum protein was one-fifth as active on the basis of nitrogen content. However iodized serum protein contains 20 per cent organic iodine (thyroglobulin contains 0.2 per cent) and on the basis of iodine content thyroglobulin is 400 times as active. This indicates that much of the iodine in iodized protein is in an inert form. The simplest explanation to account for the activation of nondescript protein by iodine is that thyronine (thyroxin minus all four iodine atoms), a physiologically inactive amino acid, is present in the protein molecule and changed to an active iodized product. Lerman and Salter have further shown that the enzymatic hydrolysis of iodized serum protein results in the formation of active and inactive peptone fractions corresponding to thyroxin peptone and diiodotyrosine peptone already described.

Physiological Actions. The primary action of the thyroid hormone is on the metabolic rate, the so-called calorigenic action. In the presence of thyroid substance, cells metabolize at a faster rate. Probably all tissue cells are affected. Apparently, the combustion of all foodstuffs is accelerated for there is no characteristic change in the respiratory quotient accompanying thyroid action.

The calorigenic action of thyroid is essential for normal growth and development. Congenital thyroid deficiency results in cretinism. In the adult, many normal functions are also dependent upon the hormone. For example, in its absence, water and salt metabolism is affected, the function of the central nervous system is impaired, muscle metabolism is altered, muscular efficiency is reduced, and circulatory disturbances are prominent. In short, the functional capacity of every tissue of the body is diminished.

The thyroid gland is also intimately related to other endocrines. The thyrotrophic hormone of the anterior pituitary is necessary for normal thyroid function. In the absence of the pituitary, atrophic changes in the thyroid occur and its secretion is diminished. Conversely hyperfunction of the anterior pituitary results in increased thyroid secretion. On the other hand, thyroid activity affects the function of other endocrine organs. Proper thyroid function is necessary for normal involution of the thymus. Hyperthyroidism leads to increased calcium excretion and parathyroid hypertrophy. The gonads are affected by hypofunction or hyperfunction of the thyroid gland. Carbohydrate metabolism is also intimately related to thyroid secretion.

Mechanism of Action. The fundamental mechanism of action of the thyroid hormone is not known. Indeed the site of action cannot be stated with any degree of certainty. Some consider that the hormone acts peripherally on individual cells, the manner of action being likened to that of a catalyst. Yet there has been no unequivocal demonstration of an increased oxygen uptake if thyroxin is added to surviving tissue slices. On the other hand, tissue slices taken from animals that have previously received the hormone show a definitely increased oxygen uptake and conversely the oxygen consumption of tissues taken from thyroidectomized animals is low. Canzanelli and Rapport (1937), however, observed that thyroglobulin added *in vitro* to slices of livers from rats and guinea pigs immediately increased the oxygen consumption. The effect was not observed with thyroxin, and the investigators therefore believe that thyroglobulin is the true thyroid hormone. Denervated organs *in situ* respond to thyroid as readily as organs having an intact innervation. The totally sympathectomized animal also responds to the hormone with an increased metabolic rate. There is evidence, however, that the spinal animal shows no increase in oxygen consumption after administration of thyroid. This indicates a central site of action and there are some who believe that thyroxin acts upon vegetative centers in the brain stem. An alleged high iodine content of the diencephalon is thought to be significant by those who adopt this point of view. The long latent period between the administration of thyroxin and its maximal action is also difficult to explain and some consider this fact an argument in favor of a central locus of action. The delayed effect is thought not to be readily compatible with the view that the action of the hormone is a catalytic one.

Thyroid Hypofunction. The body responds to an absence or deficiency of the thyroid hormone in a characteristic manner. The clinical syndrome attending marked deficiency is known as myxedema. Congenital thyroid deficiency is known as cretinism or infantile myxedema; that occurring before puberty, as juvenile myxedema; the disease in the adult, as myxedema or Gull's disease.

Adult Myxedema. Adult myxedema usually results from atrophy of the thyroid gland. The cause for the tissue atrophy is unknown. It is not the result of a lack of the thyrotrophic principle of the anterior pituitary, for in Gull's disease the pituitary is hyperactive probably in an attempt to compensate for the deficiency in thyroid secretion. Occasionally thyroid atrophy may follow hyperfunction of the gland. Myxedema may also result from complete surgical resection of the thyroid.

The *symptoms* and *signs* of thyroid deficiency are well-defined and depend for their severity on the degree of the deficiency. If this is mild, a state of hypothyroidism without myxedema may exist. This is chiefly characterized by a decrease in metabolic rate of varying degree. In true myxedema, the appearance of the patient is often diagnostic. The face is quite expressionless, puffy and pallid. The skin is usually cold and dry, the scalp scaly, and the hair is coarse, brittle and sparse, and grows very slowly. The fingernails are thickened and brittle. The subcutaneous tissue appears to be thickened. In severe cases there may be true edema. The voice is husky and low-pitched and speech is slow. Hearing is often faulty and mentality is impaired. The appetite is poor and the gastric juice tends to contain little free hydrochloric acid. Gastro-intestinal activity is diminished and constipation is common. Atony of the urinary bladder suggests that function of other smooth muscle may be impaired. Voluntary muscles are weak and flabby. Usually the heart is dilated and cardiac output is diminished. Anginal pain is frequently experienced. There may also be hydropericardium, hydrothorax and ascites. A refractory anemia, occasionally hyperchromic and macrocytic in character, is often associated with the disease. Sexual activity is diminished and in females amenorrhea is common. The patient is likely to be drowsy and to sleep a great deal. He complains of the cold in the winter but not of the heat in the summer. Many of these symptoms are probably directly related to the basal metabolic rate which may be 40 per cent below normal (Figure 108). Other signs and symptoms appear in Table 58.

The administration of adequate amounts of thyroid hormone to a thyroprivic individual usually results in an almost complete and dramatic amelioration of symptoms. A marked diuresis occurs and rids the body of excess fluid. The facial expression and speech become normal. The patient becomes more energetic, food intake increases, constipation disappears, the circulation improves and all signs and symptoms of the disease rapidly wane coincidentally with the rise of the metabolic rate. With the exception of the skin and hair, which return to normal more slowly, the individual becomes completely rehabilitated within approximately ten days. With adequate continuous therapy, symptoms do not return. The details of treatment are given under the therapeutic uses of thyroid.

Juvenile Myxedema. The symptoms and signs of juvenile myxedema are

TABLE 58

SYMPTOMS AND SIGNS OF THYROTOXICOSIS AND MYXEDEMA

(Means, 1937.)

TYPE OF HORMONE ACTION	IN THYROTOXICOSIS	IN MYXEDEMA
Calorigenic.	Sensation of warmth. Increased sweating. Warm, moist skin. Peripheral dilatation. Weight loss.	Chilliness. Decreased sweating. Dry, cold skin. Weight gain (in part).
On the circulatory system.	Tachycardia. High pulse pressure. Increased cardiac irritability. Increased cardiac output. Precordial pain.	Bradycardia. Low pulse pressure. Lowered cardiac tonus. Decreased cardiac output.
On the nervous system.	Increased irritability. Overactivity. Active cerebration. Intoxication-psychosis. Tremor. Palpitation.	Complacency. Underactivity. Slow cerebration. Sleepiness. Loss of memory. Diminished sensory acuity (sight, hearing).
On the distribution and and composition of body fluids.	Diarrhea.	Constipation. Edema, pitting and non-pitting. Edema of heart muscle. Macroglossia (?) Hyperproteinemia. Decreased blood volume. Increased deposit protein. Increased spinal fluid protein. Weight gain (in part). Albuminuria.
On tissue growth and differentiation.		Coarse skin. Coarse brittle hair. Slow skin, hair and nail growth. Anemia (?)
	Rapid growth of thyrotoxic children (?)	Dwarfism of the cretin. Immaturity of the cretin. Imbecility of the cretin.
On other endocrines.	Increased sexual activity. Oligomenorrhea-Amenorrhea.	Decreased sexual activity. Menorrhagia. Sterility. Failure to develop sex characters in the cretin and juvenile myxedema.
	Increased sensitivity to epinephrine.	Decreased sensitivity to epinephrine.
Miscellaneous.	Increased appetite. Eye signs. Myasthenia and muscular atrophy.	Decreased appetite. Hoarseness.
	Increased tolerance to certain drugs: Morphine. Low sugar tolerance. Hypocholesterolemia (?). Increased excretion of calcium and phosphorus. Creatinuria.	Decreased tolerance to certain drugs: Morphine, digitalis (?) High sugar tolerance. Hypercholesterolemia. Decreased excretion of calcium and phosphorus.

similar to the adult form of the disease except that growth and sexual development are retarded and are dependent for their resumption upon adequate therapy.

Cretinism. Cretinism has been divided into the endemic and sporadic types. *Endemic cretinism* is common in certain regions where the dietary supply of iodine is low. The thyroid may be enlarged but non-functioning or it may be atrophied. *Sporadic cretinism* is cosmopolitan in distribution, congenital in origin, and is due to prenatal atrophy or failure of embryological development. The symptoms and signs in both endemic and sporadic types are identical.

The *symptoms* and *signs* of cretinism become apparent when an infant is from three to five months of age. The child is dwarfed in size, the extremities are short, but the head is large. The face is puffy and apathetic, the color is pale yellow, the lips are thick, the tongue is large and prominent, the bridge of the nose is depressed, and the mucous membranes of the nose are thickened. The skin is dry, thick and myxedematous. Development is greatly delayed, the fontanelles do not close, the teeth erupt late, speech is retarded and the voice is deep. The heart rate is slow, appetite poor and constipation prominent.

The cretin is capable of normal development only if thyroid therapy is instituted sufficiently early in life. The details of therapy are given under the therapeutic uses of thyroid.

Thyroid Hyperfunction. Excess thyroid hormone in the body results either from hyperfunction of the gland or improper medication with the active thyroid principle. Thyrotoxicosis or toxic goiter is a term that can be applied to conditions characterized by the overproduction and excessive release of thyroid hormone. This general condition has been further subdivided into two fairly distinct clinical entities, distinguishable chiefly on the basis of the histological changes in the gland but also by certain clinical features. Exophthalmic goiter, Graves' disease and Basedow's disease are three synonymous terms for thyrotoxicosis arising from a diffuse thyroid hyperplasia whereas the term Plummer's disease has been applied to that form of thyrotoxicosis associated with focal glandular hyperplasia or neoplasia (toxic adenoma) resulting in a thyroid structure which is nodular upon palpation. Many authorities believe that no strict distinction should be made between these conditions even though certain clinical symptoms are more likely to be associated with one type than with the other.

The *symptoms* and *signs* of thyrotoxicosis in many respects are the opposite of those of myxedema. The face is often flushed and the facial expression is one of anxiety. The eyes are prominent and staring and exophthalmos is common. The patient is nervous, emotionally unstable, remains quiet with difficulty and reacts excessively to stimuli. The pulse is rapid and bounding, the pulse pressure high, the blood flow increased and commonly a systolic murmur is heard over the whole precordium. The muscles show tremors and weakness. The patient is intolerant of heat, sweats profusely and may show a low grade fever. The appetite is usually increased and the bowels are loose. Skeletal changes are not uncommon and consist of an osteoporosis resulting from the withdrawal of large amounts of calcium. In thyrotoxicosis, there is also a marked increase in sensitivity to epinephrine. Of prime diagnostic importance is the fact that the basal metabolic rate is elevated. In the average case, the rate is plus 30 to plus 60, but it may be appreciably higher. Other signs and symptoms are listed in Table 58.

Treatment of Thyrotoxicosis. The most satisfactory therapy is a subtotal surgical resection of the hyperfunctioning gland. Inasmuch as individuals with high metabolic rates are poor surgical risks, it is desirable to reduce the rate of oxygen consumption before operation. This can be accomplished temporarily by rest in bed, sedatives and the use of iodides. The relation of iodine to thyroid activity and the possible mechanism of action of this element in reducing the metabolism in thyrotoxicosis will be discussed. The dosage must be adequate for a favorable response, 0.3 cc orally once daily of a saturated solution of potassium iodide being the amount recommended by Means (1937). Iodide is also administered for several weeks after operation, and in some clinics it is continued for a year in the belief that it reduces the incidence of recurrences.

X-ray, rather than surgery, is recommended by some. The advantages of this procedure are the diminished risk, the absence of surgical trauma and the fact that the patient can remain ambulatory during therapy. According to Means (1937), about one-third of all patients respond favorably to x-ray, another third show some benefit, while in the remainder no improvement is obtained. If operation is ultimately required, surgery is often difficult due to the scarred state of the gland.

In the past, drugs have been employed to some extent in the treatment of thyrotoxicosis. Quinine hydrobromide has been used in the belief that this alkaloid can reduce the metabolic activity of tissue cells. Ergot alkaloids have been administered because of their sympatholytic action. Neither has proved of worth. The use of quinidine in the management of auricular fibrillation in thyrotoxicosis is described elsewhere.

Relation of Iodine to Thyroid Function. Normal thyroid function is dependent upon an adequate intake of iodine which is a constituent of the thyroid hormone. If iodine is deficient, the gland undergoes hypertrophy and hyperplasia. The thyrotrophic hormone of the pituitary may be the stimulus for the anatomical changes. The epithelial cells of the gland change from cuboidal to columnar and their number per given follicle greatly increases. The amount of colloid material and consequently the total iodine content of the gland are diminished. In short, the thyroid gland in iodine deficiency is a hypertrophied, hyperplastic gland, low in iodine content and functioning at maximum capacity. The metabolic rate is not low and therefore the amount of hormone elaborated is evidently sufficient.

The enlarged gland is often visible in an individual suffering from iodine deficiency; clinically this condition is known as *simple goiter* or non-toxic goiter. The hypertrophied gland may provide an adequate amount of hormone for long periods of time. On the other hand, it may become so large as to cause mechanical symptoms or as a result of hyperfunction it may undergo exhaustion atrophy and myxedema may result. If the iodine deficiency is corrected before such atrophy occurs, the gland involutes and fills with colloid. The columnar epithelium returns to its resting cuboidal state, and the gland functions normally but is still much enlarged due to its high content of colloid. Marine (1935) believes that this colloid state is the limit of involution of such a gland but Means (1937) is of the opinion that the colloid may gradually decrease and the thyroid return to normal.

Therapeutic Use of Iodine in Simple Goiter. The prophylactic administration of iodine to prevent the occurrence of simple goiter represents the chief use of the element. It is doubtful whether iodine is of benefit once the resting colloid stage has been reached, but iodine may be employed to hasten involution in the hyperplastic stage. It is prescribed in a manner similar to that for prophylaxis. If mechanical or cosmetic reasons require it, surgical resection may be necessary.

Although iodine has been used empirically for the treatment of goiter for more than 100 years, its modern use for goiter prophylaxis dates from the classical researches of Marine and his coworkers, who demonstrated the effects of iodine on experimental thyroid hyperplasia and hypertrophy. On the basis of these findings, Marine and Kimball (1917) used iodine to prevent the occurrence of goiter in a group of school children in Akron, Ohio, a region in which endemic goiter due to iodine insufficiency is prevalent. The success of their experiments led to the adoption of this type of therapy in most of the endemic goiter regions of the world.

Method of Goiter Prophylaxis. The administration of iodides in the prophylaxis of goiter is one of the cheapest and most effective of all therapeutic procedures. The most popular method of control is the use of iodized table salt. Marine

(1935) advocates one part of potassium iodide to 100,000 parts of salt, a concentration which would result in the ingestion of approximately 0.075 mgm of iodine for every 10 grams of salt intake. This is believed to be an adequate dose.

Inasmuch as iodides are relatively non-toxic and may be prescribed in large doses in certain diseases, the question may be raised as to why prophylactic iodine intake in endemic goiter regions is limited to such small amounts. The reason for this is the belief that uncontrolled iodine therapy can convert a non-toxic goiter to one of the toxic type. It must be stated that all authorities are not convinced that this is possible. It is true that in many instances a non-toxic goiter may become toxic, but the rôle of iodine in this transformation has not been established. Nevertheless the Swiss Goiter Commission is so convinced of this possibility that they limit the concentration of iodide in salt to 1:200,000.

As an alternative to the use of iodized salt, one can prescribe one-third minim per week of a solution of potassium iodide in the form of Lugol's solution. This is to be especially recommended for children and pregnant women, for during these periods proper thyroid function is essential. Means (1935) states that a dose of 250 micrograms (0.250 mgm) of iodine a day (approximately the amount obtained from the dosage of Lugol's solution cited) is certain to be adequate and in his opinion cannot possibly do harm.

Iodine Therapy in Toxic Goiter. Iodine has been used empirically in the treatment of toxic goiter for a long period of time. However, it is only in compar-

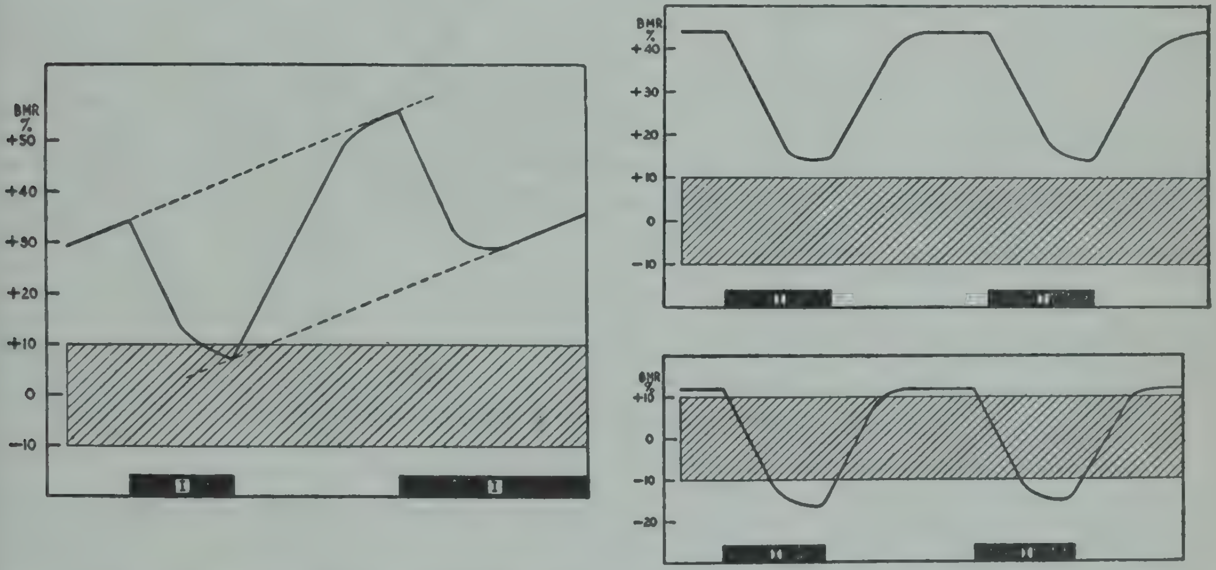


FIGURE 106. *Diagrammatic representation of the effect of iodine therapy in thyrotoxicosis.*

The cross-hatched zone is that of standard metabolic rate and the black rectangles represent periods of iodine medication. *Upper right:* Iodine administered to a patient with moderately severe hyperthyroidism causes a prompt fall in basal metabolic rate followed by a rise when the drug is omitted. A second period of iodine medication causes a similar response.

Left: When iodine is administered to a patient with hyperthyroidism which is on the upward course, a prompt fall in basal metabolic rate occurs; but when the drug is omitted there is a rise of metabolic rate to the level which would have been attained had iodine not been given. When iodine is administered a second time, the metabolic rate falls to the level which would have existed had iodine medication been continued and had the disease remained under iodine control. The upper slanting broken line indicates the trend of intensity of the disease when the patient is under full iodine control.

Lower right: The diagnostic use of iodine. A case of genuine thyrotoxicosis but with an initial metabolic rate little if at all above the standard zone. The diagnosis is in doubt and iodine medication is started. The iodine-induced fluctuations in metabolic rate may be taken as final proof of the existence of thyrotoxicosis, even though the metabolic rate never rises above what is termed "standard." (After Means, 1933. Courtesy of the *Annals of Internal Medicine*.)

atively recent years, largely as a result of the observations of Neisser (1920), Loewy and Zondeck (1921) and Plummer (1923), that this therapeutic application of iodine has been widely accepted. The response of the thyrotoxic individual to the element is striking. Within 24 hours, there is an amelioration of nearly all characteristic signs and symptoms. The metabolic rate falls at the same rate as depicted in Figure 107.

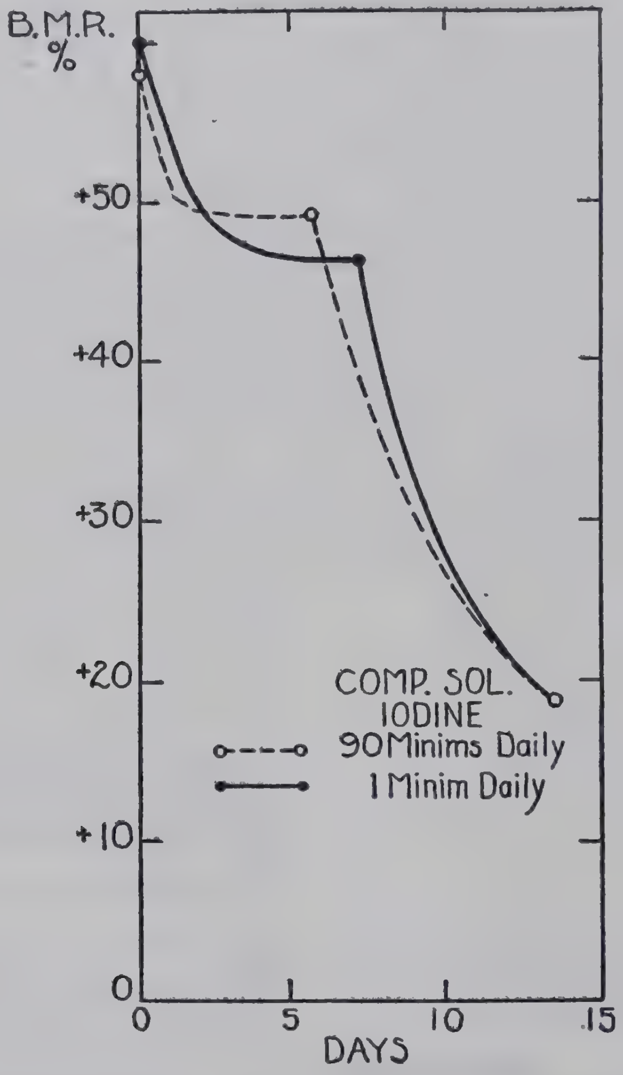


FIGURE 107. *The effect of varying doses of compound solution of iodine (Lugol's solution) on the basal metabolic rate in hyperthyroidism.*

The first reading represents the basal metabolic rate on admission; the second, after rest in bed; the third, during iodine medication. Note that as little as one minim daily of Lugol's solution is an adequate amount to produce optimal benefit within approximately one week and that no better effects are obtained from 90 times this dose. (After Thompson and Means, 1932. Courtesy of *The Journal of the American Medical Association.*)

Unfortunately, iodine therapy is not efficacious over long periods of time. The disease soon escapes from iodine control and despite continued medication, symptoms slowly return within a few weeks and are accompanied by a rising metabolic rate. The rate of return of symptoms is approximately the same as the rate of their decline. The recurrent symptoms may be intensified. Iodine therapy is therefore useless for the chronic control of thyrotoxicosis and is mainly prescribed either as a diagnostic procedure (Figure 106), or in order to cause a temporary remission in symptoms prior to surgical resection of the gland.

The dose or form in which iodine is administered bears little relationship to the response obtained. Thompson, Thompson and coworkers (1930, 1931) have found the minimal effective dose for optimal results to be six mgm of iodine daily. Increasing this amount causes no greater response (Figure 107) (Thompson and Means, 1932). Convenient forms for administration are Lugol's solution and saturated solution of sodium or potassium iodide; 0.3 cc of either preparation can be given three times daily. Larger doses may be given without undesirable effects.

Mechanism of Action of Iodine in Toxic Goiter. There are many theories as to the possible mechanism of action of iodine in toxic goiter. It would seem contradictory that a drug effective in the prevention of simple goiter should prove effective in the treatment of thyrotoxicosis. However, one should bear in mind that there is a great similarity in the histological appearance of the gland in each condition, namely a hypertrophy and hyperplasia of the secretory epithelium. In simple goiter, this is a compensatory hypertrophy resulting from an iodine want whereas in toxic goiter the reason for the histological change is unknown.

One of the older theories as to the action of iodine in thyrotoxicosis is that of Plummer (1923) who believed that the disease was due to a toxic form of thyroid hormone and that iodine changed this abnormal hormone to a less toxic and more physiological form. This theory receives no support from the modern knowledge of the chemistry of the thyroid hormone. It has been suggested that thyrotoxicosis is due to an increased responsiveness of the tissues to a normal discharge of thyroid hormone and that iodine acts to decrease the metabolic responses of the tissue cells. There is chemical evidence to indicate, however, that thyroid hormone is present in the blood of thyrotoxic individuals in excess, and it is generally accepted that thyrotoxicosis is due to an increased production of thyroid hormone. The hormone is not stored in the gland, but leaks out into the circulation. Harington (1933) has termed this escape of hormone from the gland "thyroid diarrhea." Iodine, in a manner as yet undetermined, apparently acts temporarily to stop this leakage. Accompanying its action the follicles of the gland fill with colloid, the blood concentration of the hormone falls, and symptoms are ameliorated. As the follicles distend with colloid, mechanical pressure is exerted against the epithelial secretory cells. It may be that the circulation to these cells is thereby impaired or that their transfer of hormone into the circulation is inhibited. Whether iodine acts to prevent the escape of hormone through the gland or acts chemically to stimulate the production of the colloidal storage form of thyroid protein (Salter and Lerman, 1936) cannot be stated. In support of the theory that iodine actually interrups the delivery of the hormone to the body at large, Means and Lerman (1938) showed that the initial changes in basal metabolic rate following the administration of iodine or following subtotal thyroidectomy are the same. They interpret this to signify that in each instance delivery of the hormone from the gland was interrupted and that the metabolic response obtained represented the decay curve of the hormone already present in the circulation. For additional details concerning the action of iodine the reader is referred to Marine (1927), Holst (1928) and Means (1937).

Preparations of Thyroid Hormone. Both dried thyroid gland and thyroxin are official preparations, known as *Thyroid,* U.S.P., B.P., and *Thyroxin,* U.S.P, (Thyroxine-sodium, B.P.), respectively. Thyroxin is a crystalline product of exact chemical composition, and is sparingly soluble in water. Thyroid is a yellow amorphous powder which varies somewhat in activity, but it need not be subjected to bio-assay. Rather, preparations are adjusted to contain a stated amount of iodine. The U.S.P. specifies that the iodine need only be in a form peculiar to that which exists in the thyroid gland. Official U.S.P. preparations contain 0.17 to 0.23 per cent of iodine in such form. The B.P. specifies that official preparations contain 0.1 per cent iodine in combination as thyroxin. Thyroxin contains 64 per cent iodine. As stated previously, thyroid is as active as thyroxin on the basis of iodine content. Therefore, one would expect the pure amino acid to be 320 times as active as the official U.S.P. dried whole gland, and their relative potencies actually approximate this ratio. There is also a preparation known as *Thyroxin Crude,* N.N.R., which contains 25 per cent thyroxin as the disodium salt in a partially purified form.

Choice of Preparation. Crystalline thyroxin has little or no advantage over crude thyroid preparations except that it can be used intravenously. This route of administration offers little advantage, however, when one considers the long latent period before maximum effects are obtained. So far as absorption is concerned, crude preparations are assimilated more readily and completely after oral ingestion than is crystalline thyroxin. The latter is also much more expensive.

There are several thyroid preparations on the market which contain either more or less iodine than the official U.S.P. content and therefore differ from the U.S.P. strength. The physician should make certain of the potency of the particular preparation which he employs and consider this factor in arriving at the proper dosage. Particular care regarding dosage should be exercised if any change is made in the brand of thyroid employed. The entire problem can be circumvented by using official preparations.

The practice of expressing the activity of dried thyroid in terms of weight of fresh gland can only be deplored for this gives no indication of activity or iodine content.

Absorption and Duration of Action. Thyroid is one of the few hormones active after oral administration. Both thyroglobulin and thyroxin are absorbed from the gastro-intestinal tract, the former probably in the form of active polypeptides. Crude glandular preparations are more certain of absorption than is purified thyroxin. The latter, however, can be given intravenously. Thyroxin has no speedier onset of action when parenterally administered than when given orally.

The effect of a single dose of thyroid hormone is not noticeable until 24 hours and the maximal response is delayed for about ten days, at which time the highest metabolic rate is reached. Following cessation of thyroid medication, there is a slow decline in metabolic rate and seventy days may elapse before the metabolic rate returns to its initial level (Figure 108). It is thus obvious that the daily administration of thyroid can exert a cumulative action and therefore several weeks are required before one can be certain as to the adequacy of a given dose level (Figure 1).

Therapeutic Uses of Thyroid Hormone. The specific indication for the therapeutic use of thyroid hormone is myxedema. Inasmuch as the syndrome results from thyroid hypofunction, this use represents true replacement therapy.

Adult Myxedema. According to Means (1937), "Curative treatment of adult myxedema is as perfect a form of therapy as any known to medicine. So long as he takes daily the right amount of thyroid gland, or its equivalent in some special preparation, the patient with Gull's disease can remain normal and legitimately claim his natural life expectancy." The main problem in the treatment of adult myxedema is to arrive at the proper dose of a suitable thyroid preparation. For most purposes, a U.S.P. preparation of dried thyroid dispensed in tablets is cheapest, most convenient and effective. The dose varies with the degree and duration of the deficiency and the presence of complications, especially cardiac. The object of therapy is to free the patient of symptoms. This does not necessarily mean that the basal metabolic rate must be raised to normal. Many individuals feel better when the metabolic rate remains somewhat below standard, about minus five to minus ten per cent. The average daily dose of Thyroid, U.S.P., required in myxedema is approximately 100 mgm. Seldom is the requirement greater than 200 mgm. The time of day when medication is taken is unimportant. The adequacy of dosage is checked against the patient's symptoms and metabolic rate. In this connection, it is important to recall that thyroid is slow in manifesting its activity and the final decision regarding a given dose level cannot be made until the patient has been treated for several weeks.

The patient should be carefully observed during the institution of thyroid medication. Occasionally untoward reactions such as cardiac pain, palpitation and muscle cramps are observed. This is usually an indication that therapy has been too abrupt. If such reactions occur, hormone administration should be stopped until untoward effects subside and then the dose should be built up more slowly. Death is not unknown from large doses of thyroid in myxedematous patients with heart disease.

Juvenile Myxedma. Treatment of this condition is the same as for adult myxedema except that every attempt should be made to raise the metabolic rate to the standard level and even above if adequate growth and development do not occur. The hormone should be started at a low dose level and gradually increased to the required amount. This may be as much as that required by an adult.

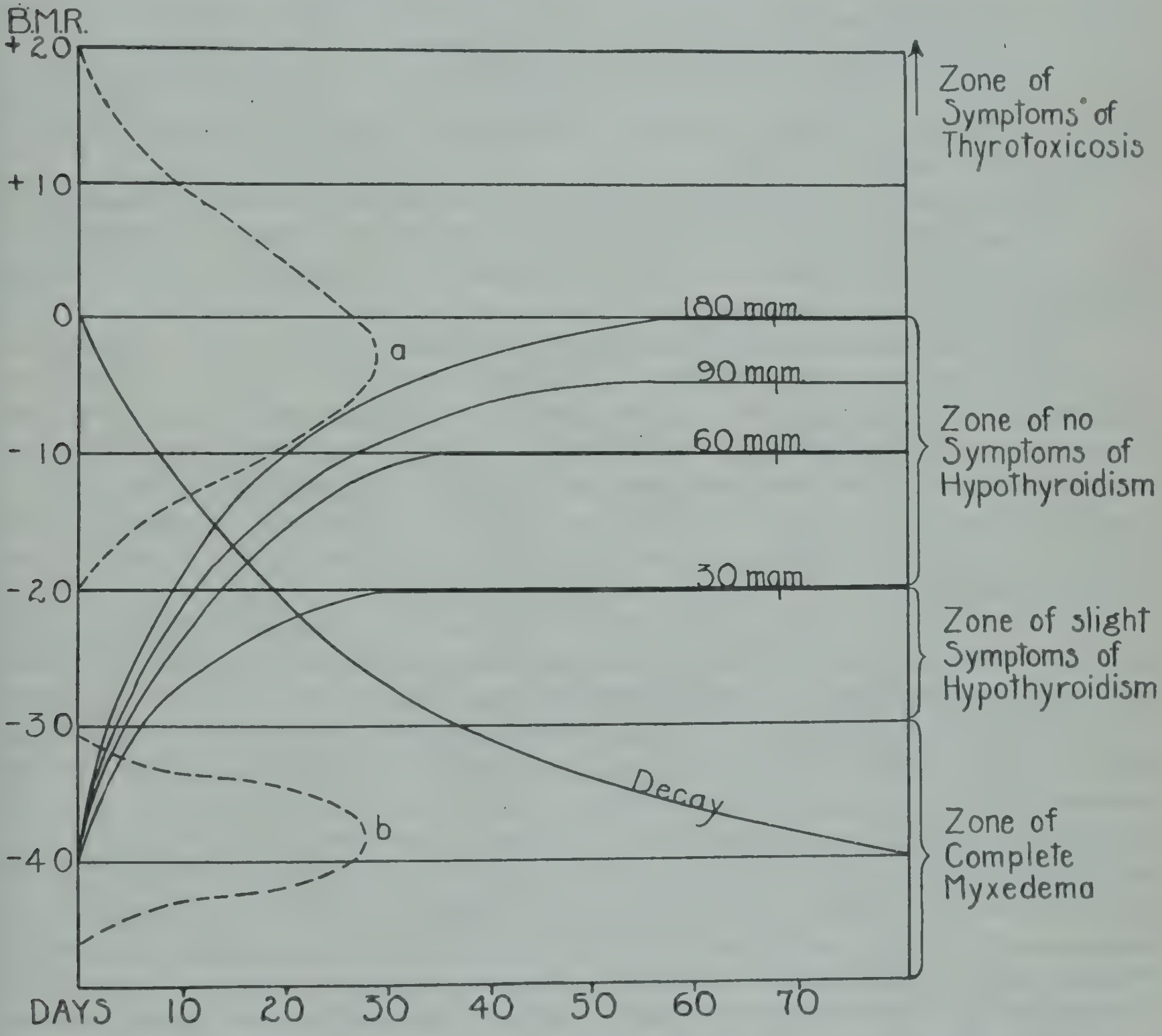


FIGURE 108. *Schematic diagram showing the approximate relationships between basal metabolic rates, severity of thyroid dysfunction and medication with thyroid.*

The dose is indicated in mgm of *Thyroid*, U.S.P., given once daily, and the curves show what may be expected in calorigenic response when patients with complete myxedema are treated. The curve labeled "*decay*" illustrates the metabolic response which may be anticipated when one discontinues the administration of thyroid to a patient with complete myxedema whose metabolic rate was maintained at a standard level, or when one completely extirpates the thyroid gland of a person with a standard metabolic rate. The frequency curves shown at the left by broken lines plotted against the basal metabolic rate depict the incidence of various levels of metabolic rate for (a) persons with no thyroid disease and (b) patients with spontaneous myxedema. (After Means and Lerman, 1935. Courtesy of the *Archives of Internal Medicine.*)

Cretinism. Success in the treatment of cretinism depends upon the age at which therapy is started. Unfortunately, many cases do not come to the attention of physicians until the retardation in development has become so obvious as to be alarming to the parents. In such cases, the detrimental effects of the deficiency may never be completely overcome. If, on the other hand, therapy is started before the age of one year, or better, before six months, there is reasonable assurance that normal physical and mental development may be obtained.

The dose of U.S.P. thyroid recommended for the treatment of cretinism is as follows (Means, 1937):

Age	*Daily Dosage*
2 to 4 months	6 mgm (⅒ grain)
4 to 8 months	12 mgm (⅕ grain)
8 to 12 months	18 mgm (3/10 grain)
12 to 24 months	24 to 45 mgm (⅖ to ¾ grain)
2 to 4 years	30 to 90 mgm (½ to 1½ grains)
4 to 12 years	60 to 180 mgm (1 to 3 grains)

Dosage should be adjusted to the particular needs of each case on the basis of symptoms and metabolic rate.

Miscellaneous Uses of Thyroid. Thyroid is used in the treatment of a number of conditions which are not characterized by a primary thyroid deficiency. The object of therapy is usually to raise a sub-standard metabolic rate in an effort to control associated symptoms.

The person who is not suffering from myxedema is usually more tolerant to thyroid than the thyroprivic individual. The latter reacts well to a small amount of hormone, and the response can usually be predicted with accuracy. In the absence of thyroid deficiency, it is difficult to predict dosage with any degree of certainty and often large amounts are given with no obvious effect. Means (1937) is of the opinion that a patient who does not have the desired reaction to 200 mgm of thyroid daily should not be given larger doses and would probably not respond to them.

Thyroid is often given to individuals with *low metabolic levels unassociated with myxedema.* It is a common practice to prescribe the hormone for any person who has a substandard metabolic rate and complains of any type of symptom. In the majority of instances no benefit is obtained but in isolated cases favorable results are noted. For example, many cases of *chronic constipation* associated with hypometabolism are benefited by the administration of thyroid in suitable dosage. Similarly *menstrual disorders* sometimes yield to thyroid therapy. *Sterility and habitual abortion* occasionally are overcome by the administration of thyroid, especially when no definite cause can be established. Good results are obtained in some cases even when the metabolic rate is found to be normal prior to therapy. Patients with certain forms of *arthritis* with low metabolic rates are sometimes relieved by thyroid medication. A particular form of refractory *vasomotor rhinitis* also is in this category. *Recurrent corneal ulcer* in patients with hypometabolism is often benefited by thyroid administration. Also certain *cutaneous lesions* associated with a dry skin and *nutritional disturbances of the nails and hair* are sometimes relieved by the hormone.

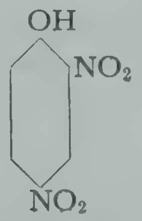
Thyroid has been extensively employed in the treatment of *obesity,* the objective being to increase the amount of foodstuff burned. By the use of the hormone, rigid dietary restriction can be avoided and this appeals to one who enjoys food to the extent that obesity is preferable to self-denial. It is questionable whether it is desirable to produce the symptoms of hyperthyroidism which of necessity must accompany the calorigenic action of thyroid when the same end-result of weight reduction can be obtained by restricting the caloric intake.

MISCELLANEOUS METABOLIC STIMULANTS

Dinitrophenol

The pharmacological actions of dinitrophenol were first noted by the French during the World War of 1914–1918 in connection with the poisoning of munition workers by the compound. The drug received little attention at that time but was reinvestigated independently by Cutting and Tainter (1932, *et seq.*) and Magne and coworkers (1932). The outstanding pharmacological action of dinitrophenol is to increase the metabolic rate, and in 1933 the drug was introduced into clinical medicine for the purpose of weight reduction. Dinitrophenol, however, was seriously misemployed, and was incorporated in a large number of weight-reducing nostrums of secret composition. Only after the drug had been widely adopted were its toxic properties fully appreciated. Although the drug rapidly came into deserved disrepute and was abandoned for clinical use, it was too late to prevent many cases of poisoning, because of the delay in onset of some of the serious effects. Unfortunately, the incorporation of dinitrophenol in nostrums persists and isolated reports of poisoning still appear.

Chemistry. Dinitrophenol (2–4 dinitrophenol) has the following structural formula:



Dinitrophenol

Other nitro compounds such as dinitrocresol have similar metabolic effects provided the relative position of the two nitro groups is retained.

Pharmacological Actions. Aside from its toxic effects, the main action of dinitrophenol is on the metabolic rate, the other responses to the drug being incidental to the increased oxygen demand.

Metabolic Effects. Dinitrophenol increases the rate of tissue metabolism. It is believed that the drug acts directly on the cell, possibly in the capacity of a ferment, to increase the oxygen uptake. Increased metabolism can be demonstrated after dinitrophenol both in intact animals and in isolated tissues. The onset of action is immediate, and can be observed within one minute after the intravenous injection of the compound. After the oral ingestion by human beings of from three to five mgm per kilogram, the metabolic rate rises within an hour to from +20 to +30 per cent and remains at this level for about 24 hours. It then gradually returns to normal within the following 48 hours. If the aforementioned dose is repeated daily, the metabolic rate rises to approximately +50 per cent and remains at that level as long as medication is continued.

The response to dinitrophenol differs from that to thyroid and therefore the increased oxygen consumption cannot be considered physiological in nature. For example, whereas thyroid increases the oxidation of all foodstuffs, dinitrophenol selectively increases the oxidation of fat, as evidenced by the fall in respiratory quotient. The rise in oxygen consumption is not accompanied by an increase in heart rate or cardiac output, and it is only after anoxia becomes evident that circulatory changes are observed. Respiratory exchange, however, is markedly increased. The fundamental difference in action between dinitrophenol and thyroid can also be appreciated from the fact that the symptoms of myxedema are not relieved by the former drug, despite the fact that the metabolic rate may rise toward normal figures. Neither does dinitrophenol accelerate developmental processes as does the hormone of the thyroid gland.

The increase in metabolic rate is proportional to the dose of dinitrophenol, and levels as high as ten times normal may temporarily be reached. However, with high metabolic rates, heat production so exceeds the physiological capabilities of heat dissipation that fatal hyperthermia may result. A dose of 10 mgm per kilogram in human beings can raise the rectal temperature three degrees Centigrade.

Absorption, Fate and Excretion. Dinitrophenol is readily absorbed from the gastrointestinal tract. It circulates as the sodium salt, which is a yellow dye that may impart a yellow color to the body fluids and tissues. Solutions of the soluble sodium salt may also be injected hypodermically. The drug is excreted by the kidney, partially unchanged and partially in the form of the reduction product, 2-amino, 4-nitrophenol.

Toxic Actions. Acute poisoning from dinitrophenol or dinitrocresol runs a rapidly fatal course, the signs and symptoms being nausea, gastric distress, restlessness, sensation of heat, flushed skin, sweating, deep and rapid respiration, fever, cyanosis, anoxia and death, followed by almost immediate rigor mortis. Treatment consists in the use of an ice bath to reduce the patient's fever, the administration of oxygen to assure maximal oxygenation of the blood, and the injection of large amounts of isotonic sodium chloride solution to replace the fluid and electrolyte lost by sweating.

The chronic administration of dinitrophenol leads to untoward reactions in a significant percentage of patients. These include various types of skin lesions, peripheral neuritis, agranulocytosis, anemia, purpura, generalized pain and weakness, gastro-enteritis, anorexia and vomiting, and damage to parenchymatous organs, especially the liver and kidneys. The eye is also vulnerable and cataracts may develop from one to many months after medication with dinitrophenol. The incidence of cataracts has been estimated at one per cent of patients taking the drug. They may develop long after medication has ceased.

Therapeutic Uses. Due to the high incidence of toxic reactions, dinitrophenol should never be used in therapy. The drug was of value only in the treatment of obesity, a condition which responds satisfactorily to safe therapeutic measures and in which the use of a toxic agent is unwarranted.

Miscellaneous Metabolic Stimulants. There are many drugs which increase the basal metabolic rate by a secondary action, the drugs having other more important properties. As examples may be mentioned epinephrine and various sympathomimetic compounds, cocaine, caffeine, etc. A metabolic stimulant which has been extensively employed in the laboratory is *beta-tetrahydronaphthylamine*. The drug is a potent pyretic but has no therapeutic applications.

THYROID

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CHAPTER 64

PARATHYROID

Historical. The earliest extirpations of the parathyroid glands were performed accidentally in the course of thyroidectomies. The resulting symptoms were attributed to the loss of thyroid tissue. Death following experimental thyroidectomy and the unwitting removal of the parathyroids was probably first recorded by Raynard (1834–35) who observed that whereas older dogs survived thyroidectomy, puppies succumbed within a few days after the operation. Later investigators outlined in detail, with no appreciation of the cause, the symptoms now associated with parathyroidectomy.

Although there were many earlier references to the yellow glandular bodies attached to the thyroid, credit for the discovery and the description of the parathyroid glands is usually given to Sandstrom (1880), who published an anatomical report that excited little attention among physiologists. The glands were rediscovered by Gley in 1891 who determined the effects of their extirpation. In Gley's and subsequent studies, the symptoms following parathyroidectomy varied so greatly in different species that the importance of the organs was not appreciated and controversies continued as to whether they were essential to life. Identification of the internal and accessory parathyroids was finally accomplished, accounted for the discrepancies in experimental results, and led to the realization of the true importance of this endocrine gland.

MacCallum and Voegtlin (1909) first noted the effect of parathyroidectomy on the level of serum calcium. Inasmuch as Howell (1899) and Loeb (1901) had previously established the physiological importance of the calcium ion, the relation of low serum calcium to parathyroprivic symptoms was quickly appreciated and a comprehensive picture of parathyroid function began to form. Attempts were then made to obtain active extracts of the gland and success was finally attained (Berman, 1924; Hanson, 1925; Collip, 1925). It was readily demonstrated that active extracts could alleviate hypocalcemic tetany, and raise the serum calcium level in normal animals. For the first time the relation of parathyroid hyperfunction to certain definite clinical abnormalities was appreciated.

Chemistry. Comparatively little is known of the chemistry of the parathyroid hormone, for even the most purified preparations are still quite crude from a chemical standpoint. All evidence points to the fact that the hormone is a protein. It gives characteristic protein reactions, is nondialyzable, and activity is lost after hydrolysis with acid or alkali or after digestion with proteolytic enzymes. If the active principle is slowly hydrolyzed with dilute acid, the increase in free amino groups parallels a decrease in hormonal activity. Treatment with weak alkali leads to the production of ammonia and a marked reduction in activity (Tweedy and coworkers, 1936).

Hypoparathyroidism. Extirpation or hypofunction of the parathyroids leads to a characteristic syndrome. Symptoms are due to chemical changes in the blood consisting of a fall in calcium and a rise in phosphate concentration. Accompanying the blood changes is a decrease in renal excretion of these ions. Following removal of the parathyroids in dogs, there is first noticed a gradual loss of appetite, and food given by stomach tube is vomited. Fine fibrillary twitchings of the muscles develop and soon become coarser. The animal shows a characteristic awkward gait. Symptoms become progressivly worse and terminate in convulsions which may follow in rapid succession or occur at intervals of several days. During the convulsion body temperature is usually markedly elevated and breathing is rapid and shallow. Death follows respiratory failure which probably results from spasm of the muscles of the larynx and diaphragm.

The symptoms enumerated are mainly the result of hyperirritability of the peripheral neuromuscular mechanism as shown by an increased sensitivity to electrical stimulation. That the disturbance is of nervous rather than muscular origin is indicated by the fact that the spasms can be abolished by curare. At one time it was thought that a toxic element in the blood was responsible for the convulsive symptoms of hypoparathyroidism. Experimental evidence was offered that guanidine was the specific toxic agent involved. It is now generally agreed, however, that the derangement in neuromuscular function results from the decrease in the concentration of ionized calcium in the blood.

Clinical Hypoparathyroidism. Tetany arising from a lowered blood calcium is often encountered clinically. The basic causes leading to abnormalities in calcium metabolism are discussed under the pharmacology of calcium. Hypocalcemia seldom is due to abnormal parathyroid function. The occasional cases which occur usually follow operative procedures either on the thyroid gland or the parathyroids themselves. More rarely, disease of the parathyroids is the cause. If the degree of hypofunction is not too great, a condition of *latent tetany* may exist for long periods. The diagnosis of latent tetany can only be established by determining the sensitivity of peripheral nerves to mechanical or electrical stimulation. The earliest symptoms of *manifest tetany* take the form of paresthesias in the extremities. These are followed by muscle spasms, which frequently take the form of carpopedal spasm and laryngospasm. Eventually, generalized convulsions occur. It is highly probable that the neuromuscular mechanism of smooth muscle is also affected. For example, attending hypocalcemia there may be spasm of the ciliary muscle, iris, esophagus, intestines, urinary bladder and bronchi. A marked tachycardia indicates that the heart is also involved. Vascular spasm in the fingers and toes is also commonly observed. In *chronic tetany,* ectodermal changes consisting of a loss of hair, grooved and brittle finger nails, defects of the dental enamel and cataracts are frequently encountered.

Hyperparathyroidism. Hyperparathyroidism results either from parathyroid hyperfunction or from the injection of parathyroid extract. If a single large dose of extract is injected into an experimental animal, characteristic changes occur in the blood chemistry. The concentration of ionized calcium in the blood increases markedly, reaching values as high as 18 to 20 mgm per cent in 12 to 18 hours. This is accompanied by a slight decrease in the concentration of blood phosphate. Attending the blood changes there is a marked diuresis. Initially, phosphate and chloride are excreted in excess in the urine; later, large amounts of calcium are eliminated. As a result, the excretion of calcium and phosphate is increased many times above normal and a negative balance of these ion occurs.

When repeated injections of parathyroid extract are given to animals, toxic symptoms are noted. The blood calcium concentration rises to 20 mgm per cent, but after reaching its peak it slowly declines despite the fact that hormone is being repeatedly injected. An initial diuresis results and the urine contains large amounts of calcium and phosphate. Diuresis soon stops abruptly, however, and is then followed by oliguria and anuria. The animals exhibit anorexia, vomiting, diarrhea and muscular atony and death in uremic coma occurs. The sudden failure of renal function in all probability results from severe anhydremia produced by the diuresis, vomiting and diarrhea. Thus the primary cause of death is shock due to the large reduction in blood volume.

The chronic administration of parathyroid extract to experimental animals leads to a marked disturbance in calcium metabolism evident in the osseous and soft tissues. Bone is decalcified and bone cysts, deformities and spontaneous fractures occur. The calcium mobilized from bone is precipitated in the soft tissues. Metastatic calcification is observed especially in the kidneys, the walls of the stomach and bronchi, the interstitial connective tissue, the heart muscle and the medial coats of the lesser arteries.

Clinical Hyperparathyroidism. Clinical hyperparathyroidism results from hyperfunction of the parathyroid glands. Seldom does improper medication cause the severe syndrome described, for the warning signs are too obvious to be long ignored. Anorexia, vomiting and diarrhea require discontinuance of therapy. When parathyroid extract is used clinically, the level of blood calcium should be closely followed and not allowed to rise too high. If toxic symptoms result, however, treatment is directed toward maintaining an adequate volume of extracellular fluid and avoiding the occurrence of shock.

Hyperfunction of the parathyroids leads to a condition know as *osteitis fibrosa cystica* or *von Recklinghausen's disease,* the symptoms of which are similar to those observed in animals when large amounts of extract are injected. The calcium of the blood is markedly elevated, bones are decalcified and abnormal, metastatic calcification occurs, and polyuria is evident. In the clinical condition, however, diuresis is not followed by oliguria, probably because the extracellular fluid volume is maintained by an increased ingestion of water and electrolytes. Osteitis fibrosa cystica is best treated by irradiation or partial extirpation of the hyperfunctioning parathyroid glands (Figure 109). Following surgical procedures, however, parathyroprivic tetany may ensue.

Mechanism of Action. The exact mechanism of action of parathyroid hormone is unknown. How extirpation of the gland reduces and administration of active extract increases the concentration of diffusible calcium in the blood remains to be elucidated. Some believe that the primary effect of parathyroidectomy may be on the metabolism of phosphate and that the increase in the concentration of this ion in the blood may be the causative factor in the reduction of available ionized calcium. The marked phosphate diuresis which occurs soon after injection of parathyroid extract (Figure 110) has given rise to the suggestion that the hormone acts directly on the kidney and that hypercalcemia is secondary to the reduction in blood phosphate (page 600).

Parathyroid extract does not alter greatly the intestinal absorption of calcium and phosphorus, but rather it mobilizes calcium from the bone. That the skeleton is the source of the excess calcium is evidenced by the marked negative balance of the ion and the histological changes which occur in the bones. (*See* also the discussion under vitamin D and dihydrotachysterol.)

Preparations, Bio-assay and Unitage. *Solution of Parathyroid,* U.S.P., is the official preparation available. Bio-assay to determine its activity is performed on healthy male dogs weighing 10 to 12 kg. One unit of hormone is one one-hundredth the amount necessary to raise the level of serum calcium one mgm per cent within 16 to 18 hours after subcutaneous injection. Preparations are adjusted to contain approximately 100 units per cc.

Absorption, Fate and Excretion. Solution of parathyroid must be given parenterally, for gastro-intestinal absorption of the active principle is precluded by enzymatic destruction. The usual route of administration is subcutaneous but in emergencies a more rapid response can be obtained by intravenous injection. The fate of the hormone is not known but the duration of activity is long. Maximal effects are obtained approximately 18 hours after a single injection and the response may last for 36 hours. Therefore when the hormone is used for chronic medication it is not injected more often than once daily or on alternate days.

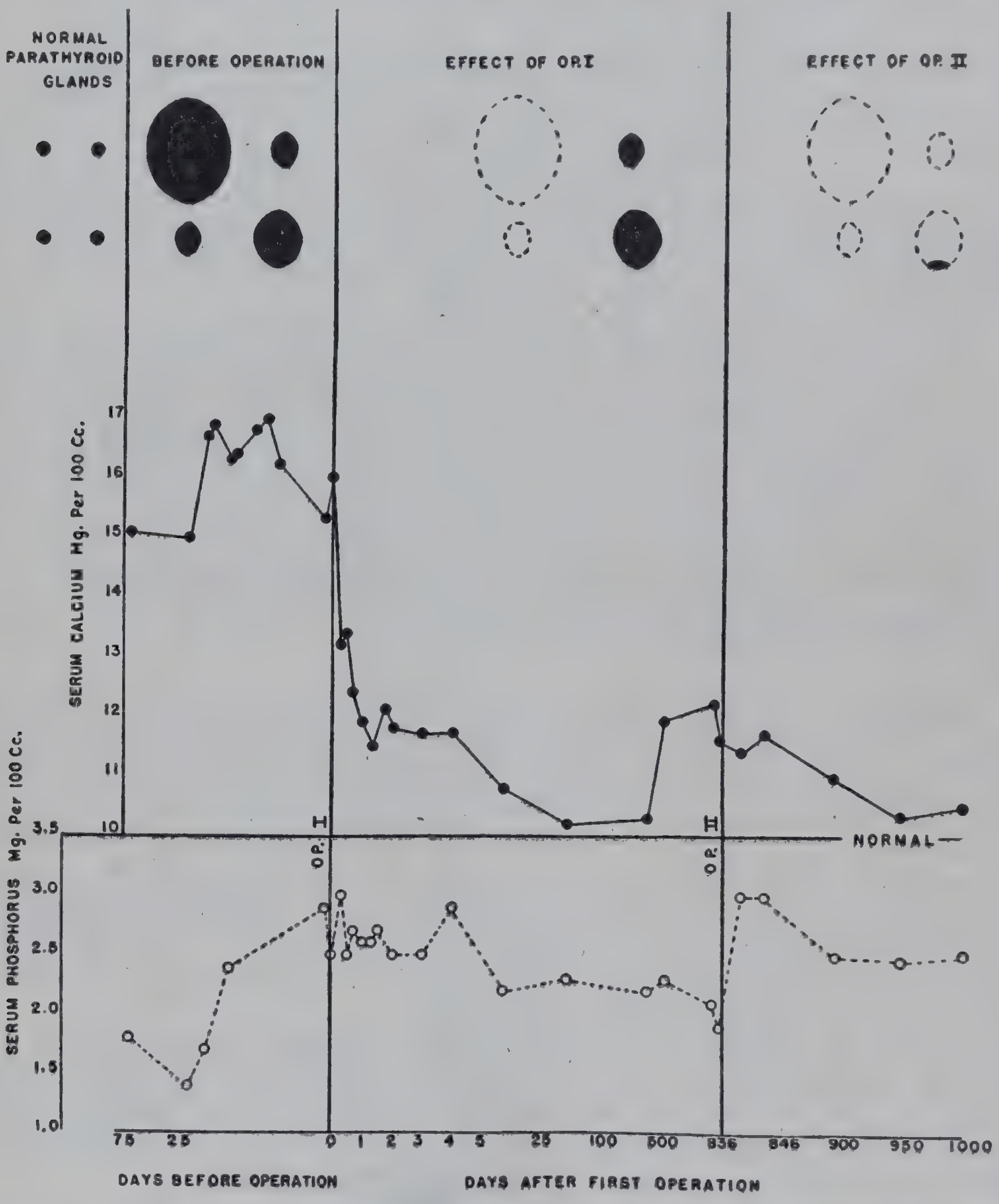

FIGURE 109. *The effect of parathyroid resection on the serum calcium and inorganic phosphorus in hyperparathyroidism.*

Male, aged 26, entered the hospital complaining of renal colic, polyuria and polydipsia. Serum calcium and phosphorus values were 15.1 and 1.8 mgm%, respectively. No skeletal involvement. Renal calculi removed at operation. Note the marked and immediate reduction of the elevated serum calcium which occurred after the operative removal of 15.6 grams of parathyroid tumor. Because the operation was unilateral, symptoms returned due to residual tumor tissue. A subsequent further resection permanently controlled the condition. (After Albright, Sulkowitch and Bloomberg, 1938. Courtesy of the *Archives of Internal Medicine*.)

Therapeutic Uses. Parathyroid hormone must be used with discretion and with a full appreciation of its mechanism of action. With rare exceptions, it is employed only in those conditions in which there is hypocalcemia. Furthermore, therapy with the hormone is not without danger and close attention must be paid to the patient and the blood calcium and phosphate values. For these reasons, hospitalization is highly desirable. Of paramount importance is the knowledge that many disturbances in calcium metabolism are not related to abnormal parathyroid function and readily yield to proper diet.

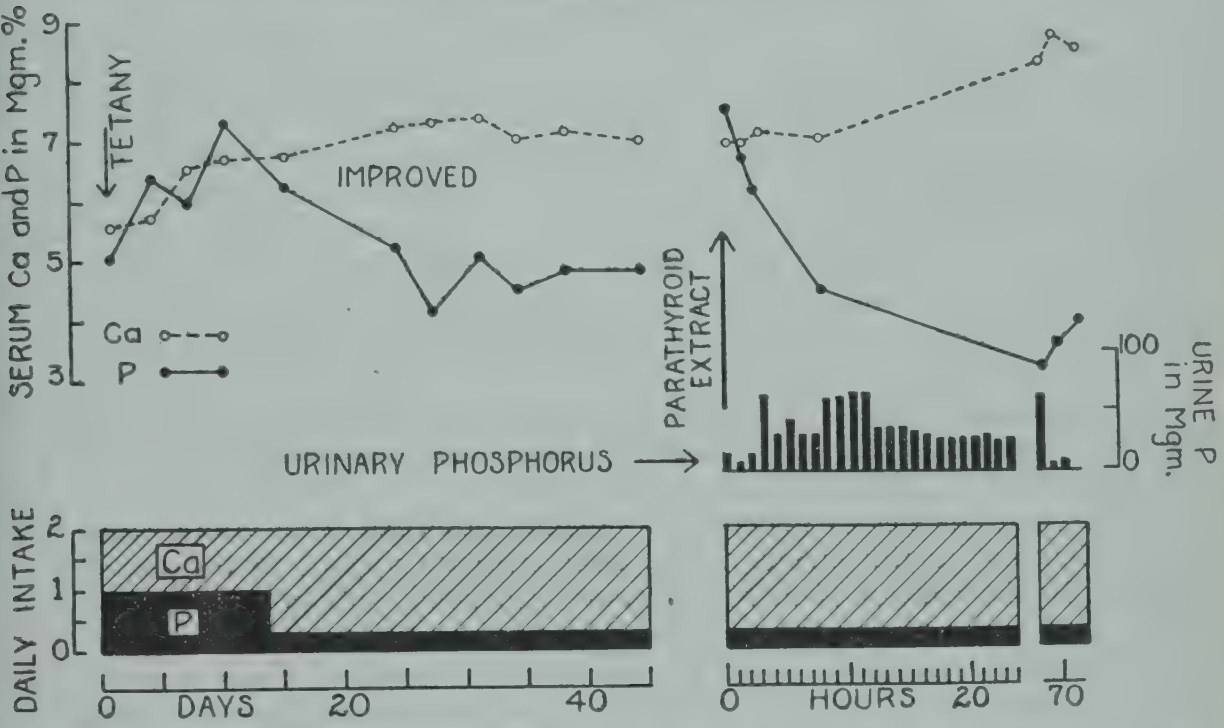

FIGURE 110. *Therapy of hypoparathyroidism by diet and parathyroid extract.*

Negress, aged 36, hypoparathyroidism following a partial double thyroidectomy. On admission, the patient had typical pedal spasm, positive Chvostek and Pool signs, and a positive Trousseau test in less than a minute. The serum calcium and inorganic phosphorus were 5.5 and 5.2 mgm%, respectively. Dietary treatment with a daily calcium intake of 2.0 grams and a phosphorus intake of 1.0 gram failed to relieve symptoms or alter the blood chemistry significantly. Reducing the phosphorus intake to 0.27 gram daily caused a moderate rise in the level of serum calcium and a fall in serum phosphorus. Phosphate must have been lost in the feces in the form of calcium phosphate inasmuch as little appeared in the urine. Symptoms were relieved. In contrast with the slow response to dietary therapy, note the rapid change in the chemistry of the blood brought about by the intramuscular injection of 80 units of parathyroid extract. The serum phosphate fell precipitously, largely as a result of excretion of phosphate in the urine. There was a concomitant rise in the concentration of serum calcium, and evidence of latent tetany disappeared. Parathyroid extract should be reserved for the purpose of bringing the patient under initial control, and therapy should be continued if possible with proper dietary management. (After Shelling and Goodman, 1934. Courtesy of *The Journal of the American Medical Association.*)

Hypoparathyroidism is the specific indication for hormonal therapy. If the level of blood calcium is markedly depressed and tetany severe, as much as 100 units of the extract may be injected at once or in divided doses without danger of producing hypercalcemia. In less drastic cases, 10 to 20 units suffice. Because the onset of action of the hormone is slow, it is usually necessary to give immediate relief to the patient by the intravenous administration of a calcium salt. If the diagnosis is uncertain or calcium is not available, symptomatic treatment of convulsions with central nervous system depressants may be needed. Once the tetany has been brought under control, every effort is made to prevent its recurrence by dietary therapy and thus relieve the patient of the inconvenience and danger frequent injections of hormone. As has already been stated, the changes in th blood chemistry which result from hypoparathyroidism consist of a lowering serum calcium and an increase in serum phosphate. Therapy should therefor center upon insuring a dietary intake low in phosphorus and high in calciu (Figure 110). This requires a diet rich in fruits, vegetables, fats and carbohydrates and poor in meats, glandular tissue, nuts, cheese, milk and egg yolk In addition, calcium preparations may be given by mouth. This phase of treatment has been discussed in detail by Shelling (1935).

Dihydrotachysterol is also effective in the therapy of hypoparathyroidism The drug has the advantage that it can be given by mouth and it is probably safer preparation to use than parathyroid extract. Albright (1939) described the technic of its administration, and the use of a simple test for urinary calcium which obviates the necessity for routine blood calcium determinations. The patient himself can thus judge the proper dose of dihydrotachysterol. The initial dose is three cc a day (*see* page 1289 for preparation) and this is reduced to a maintenance level of one cc three to five times weekly as soon as calcium appears in the urine. The pharmacology of dihydrotachysterol is discussed elsewhere.

Manifest tetany resulting from disturbances in calcium metabolism unrelated to parathyroid function are occasionally treated unnecessarily with parathyroid hormone. *Infantile tetany* associated with rickets responds well to calcium and vitamin D therapy. Although parathyroid extract relieves the symptoms of hypocalcemic tetany, its efficacy depends on calcium mobilized from bones which are already deficient in this element. The same criticism applies to the use of the hormone in the control of manifest tetany associated with *osteomalacia, celiac disease* and *sprue.* Nor is the hormone indicated in *gastric tetany,* a condition which is more rationally treated by the administration of calcium and acid-forming salts to correct the disturbances in the acid-base equilibrium caused by prolonged vomiting. The occasional case of manifest tetany associated with *pregnancy* and *lactation* also is best treated by parenteral calcium followed by dietary control.

There is no rationale for the use of parathyroid extract in conditions characterized by hyperexcitability of the nervous system unassociated with disturbances in calcium metabolism. Unless there is definite evidence of hypocalcemia, the use of parathyroid extracts in such conditions as epilepsy, chorea minor and eclampsia is contrary to all principles of sound therapeutics.

Parathyroid hormone has had some vogue in the control of hemorrhagic conditions because of the important rôle which calcium plays in the blood clotting. Good results with it have been claimed in the treatment of *hemorrhages* associated with chronic ulcerative colitis, pulmonary tuberculosis, menorrhagia, uterine fibroids, and post-tonsillectomy. The hormone has not proved effective in the treatment of such conditions as hemophilia, purpura hemorrhagica and hemorrhage of the newborn. The best results have been obtained when the calcium level of the blood is increased only slightly by therapy and marked hypercalcemia is avoided. According to Shelling (1935), if hemostatis does not occur after three or four injections of 15 to 30 units, continued therapy with parathyroid hormone is usually futile.

Parathyroid hormone is also used in the treatment of *lead poisoning* (page 730) and *resistant edemas* (page 643).

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CHAPTER 65

ANTERIOR PITUITARY AND ANTERIOR PITUITARY-LIKE HORMONES

The anterior pituitary has been termed the "master hormone" of the body. Conclusive evidence is accumulating that, in addition to its own specific functions, this endocrine gland regulates the activities of the other organs of internal secretion, and that many hormonal diseases are essentially anterior pituitary disorders. The therapeutic application of this knowledge must await chemical advances. Apparently the anterior pituitary gland is the source of what may prove to be nine or more separate hormones. Seemingly they are protein in nature and therefore difficult to separate and isolate in pure form. Commercial preparations are comparatively crude in that they contain a mixture of hormones and their pharmacological activity leaves much to be desired. The difficulty and expense of obtaining the gland on a commercial scale also hinder the development of therapeutically useful anterior pituitary substances. The pharmacology of the gland for these reasons is poorly understood.

The Hormones of the Anterior Pituitary. At least nine separate types of activity have been attributed to the anterior pituitary. It is not justifiable to state that nine distinct hormones produce these actions because a single chemical substance may be responsible for several effects. As each new physiological rôle of the anterior pituitary is elucidated, attempts are made to isolate chemically the substance responsible, uncontaminated by other constituents. In many instances success has rewarded these efforts, but there is no assurance that in the process of isolation an original pituitary hormone, less discrete in activity, may not have been altered or fragmented. One must recall in this connection that there are only three recognized types of cells in the anterior hypophysis which can conceivably secrete chemical entities. To limit the possible number of hormones on this basis, however, is unjustified because there is no evidence that the complex activities of a cell may not elaborate more than one chemical secretion.

The following are the so-called hormones of the anterior pituitary: (1) growth, (2) gonadotrophic, (3) lactogenic, (4) thyrotrophic, (5) adrenotrophic, (6) parathyrotrophic, (7) diabetogenic, (8) ketogenic, (9) pancreatrophic. In addition, several other hormones affecting carbohydrate metabolism have been described. None of the hormones is commercially available in pure form. For example, available commercial preparations of growth hormone contain gonadotrophic and thyrotrophic principles and traces of others. That this is an unfortunate mixture can readily be appreciated when one considers the problem of the treatment of a young child who is a pituitary dwarf. In the process of restoring growth by hormonal therapy there is the possibility of inducing both puberty and hyperthyroidism.

GROWTH HORMONE

Historical. The growth hormone is secreted by the acidophilic cells of the anterior pituitary. Its presence had long been suspected from clinical observations. Minkowski (1887) associated acromegaly with hyperfunction of the anterior lobe of the hypophysis and Paltauf believed dwarfism to be associated with an abnormality of the gland. The development of neurosurgical technic made possible physiological experimentation on the function of the pituitary. Aschner (1909) demonstrated that hypophysectomy in dogs resulted in dwarfing. Many subsequent investigations substantiated this original work. It was not until 1921 that the positive side of the activity of the growth hormone was experimentally demonstrated by Evans and Long. These investigators produced gigantic rats by injecting extracts of the anterior hypophysis. Subsequently the observation was extended to other species.

Chemistry. The growth hormone is apparently a protein. It is destroyed by heat and any harsh chemical procedure that denatures or hydrolyzes the protein molecule. Due to the fact that the other hormones of the pituitary are of a similar chemical nature, the substance promoting growth has not been isolated in pure form. Preparations invariably show some thyrotrophic, lactogenic and gonadotrophic activity. This has led some investigators to believe that the growth hormone is not an entity but that growth, in so far as it is dependent on the anterior hypophysis, is the result of the combined action of several of the pituitary principles.

Hyposecretion of the Growth Hormone. Deficiency of the growth hormone during the period of somatic development causes a condition known as pituitary dwarfism. The deficiency may be due to a congenital absence of the acidophilic cells of the pituitary or a destructive lesion of the gland. The symptoms and signs of pituitary dwarfism vary considerably depending upon the age at which hypofunction occurs. If it originates late in the second decade, physical changes are difficult to detect; but a congenital pituitary abnormality dramatically arrests growth and development. The body of a pituitary dwarf is diminutive yet fairly well proportioned. The features are small and poorly defined. The internal organs are even proportionately smaller than the body. Dentition is markedly retarded. Usually no sexual development takes place and even in adult dwarfs the genitals are undeveloped, the voice is high pitched and child-like and there is an absence of axillary and pubic hair. Intelligence may be fairly normal. In the event that the gonadotrophic hormone is not involved, sexual development may take place. Such dwarfs are then fertile and may be capable of producing normal offspring.

Pituitary Cachexia or Simmonds' Disease. Although this syndrome is discussed in connection with the growth hormone, it is characterized by a deficiency of all the anterior pituitary hormones. Pituitary cachexia is a rare disease resulting from a destructive process involving the anterior pituitary. It is more common in females and the onset often follows childbirth. Simmonds, who first described the condition in 1914, attributed this finding to the fact that the anterior hypophysis is likely to be injured following post partum involution. The extensive symptomatology probably results from the fact that many endocrine glands are impaired due to pituitary hypofunction. Weight loss is marked, microsplanchnia develops, the skin becomes wrinkled, yellowish and dry, axillary and pubic hair falls out, the teeth become carious and loose, the jaw atrophies, the metabolic rate declines, hypothermia is pronounced, sexual function is absent and mental apathy is severe. Treatment is discussed below.

Hypersecretion of the Growth Hormone. Hypersecretion of the growth hormone results from increased secretory activity of the acidophilic cells of the anterior pituitary. Enlargement of the gland is usually present and results from a marked hyperplasia of the acidophilic cells. An acceleration in growth occurs and the clinical condition which develops depends upon the time of onset in relation to the normal cessation of growth.

Acromegaly. In the event that acidophilic hyperplasia occurs after normal growth and development have ceased, the most marked changes are noted in the skeleton, all the bones of which are affected. The long bones increase in length and diameter, and the flat bones in thickness. The hands become particularly large and broad and the fingers puffed. The feet also increase greatly in size. The paranasal sinuses and vertebrae are much enlarged and the cartilages of the body become calcified. The mandible enlarges and gives to acromegalics a characteristic "lantern-jawed" appearance. Mandibular growth may be so extensive that complete malocclusion of the teeth results. Excessive growth is not confined to the skeleton. The tongue becomes uncomfortably large and there occurs so extensive a splanchnomegaly that the size of the viscera is out of proportion to the rest of the body. It is not definitely known whether the increase in organ size is due to cellular hypertrophy or hyperplasia. In experimental animals receiving large amounts of growth hormone, the tissue cells are normal in size but greatly increased in number. The function of other endocrine glands is also disturbed. The thyroid and adrenals are definitely enlarged. This may result from increased secretion of the specific trophic hormones or merely be a reflection of the general excess growth. Carbohydrate metabolism is disturbed as evidenced by the high incidence of glycosuria among acromegalic individuals. Other common symptoms are increased basal metabolic rate, headache and visual changes. Sexual function is greatly disturbed.

Pituitary Gigantism. This condition is distinguished from acromegaly in that hyperfunction of the anterior pituitary coincides with the normal prepuberal growth period. The result is a more symmetrical type of growth. For example, the abdominal viscera are large, but not out of proportion to the rest of the body. Skeletal growth is so great that a height of over eight feet may be attained.

Treatment. In both acromegaly and gigantism treatment consists either of roentgen irradiation of the pituitary gland or surgical removal of a portion of the hyperplastic tissue. Both procedures can successfully arrest the progress of the disease. In the event that cellular hyperplasia has resulted in a tumor sufficiently large to cause marked pressure symptoms, surgical intervention is usually necessary.

Absorption and Route of Administration. The growth hormone is readily absorbed after parenteral administration. The hormone is valueless when administered orally because it is destroyed in the alimentary tract.

Preparations and Bio-assay. Growth hormone preparations are not official and have not been accepted for inclusion in N.N.R. There are several, however, which are commercially available. These possess, in addition to the growth hormone, appreciable thyrotrophic and gonadotrophic activity. The preparations are assayed only for their effect on the growth of rats and therefore one cannot anticipate the extent of clinical side-actions. Furthermore, there is no standard unit for expressing the potency of the preparations. No two preparations have the same basic unitage and the physician must accept the recommended dose or determine by trial and error the amount he should use. Preparations containing the growth hormone are Anterior Pituitary Extract (Squibb) and Antuitrin-Growth (Parke, Davis & Co.).

Therapeutic Uses. The specific use for the growth hormone is in the treatment of pituitary dwarfism. Successful results have followed this type of replacement therapy, but it must be emphasized that therapy is still in the experimental stage and that the use of growth hormone preparations should be left to experienced endocrinologists. For example, in treating a young pituitary dwarf, there is real danger of producing thyroid hyperplasia, with its attendant effects on growth and development, and of inducing premature adolescence because of the presence of thyrotrophic and gonadotrophic hormones in the commercial preparations. Nevertheless, there is little doubt that once the diagnosis of dwarfism of pituitary origin is established the available therapy should be given despite these disadvantages. Successful results have been reported by Taylor (1938), Lawrence and Harrison (1938), and Molitch and Poliakoff (1938).

Anterior pituitary extract is also employed in the treatment of Simmonds' disease. Here the presence of thyrotrophic and gonadotrophic hormones in the commercial preparations is advantageous for one is treating a multiple deficiency encountered in adults. In addition to anterior pituitary extract, desiccated thyroid and specific gonadotrophic hormone preparations are employed.

GONADOTROPHIC HORMONE

History and Function. The functional relationship between the anterior pituitary and the gonads was recognized following the earliest experiments on hypophysectomized animals. Crowe, Cushing and Homans (1910) recorded the the loss of gonadal activity following extirpation of the pituitary in the dog. Evans and Long (1921), in experiments already cited, produced gigantism in rats by injecting anterior pituitary extracts and observed excessive luteinization of the ovaries. Subsequent investigations even more definitely ascribed to the anterior pituitary an important function in initiating puberty and regulating the cyclic activity of the sex glands. It is now recognized that all aspects of ovarian activity are under anterior pituitary control, for this master gland secretes one substance which stimulates maturation of the Graafian follicles and the liberation of estrin, and another which brings about luteinization of the ruptured follicle and the production of the hormone of the corpus luteum, progesterone. These two substances are known as the follicle-stimulating hormone, FSH, and the luteinizing hormone, LH, respectively. In the male, the follicle-stimulating hormone induces spermatogenesis and the development of the seminiferous tubules while the luteinizing hormone acts upon the interstitial tissue of the testes and stimulates production of the male sex hormone, testosterone.

Chemistry. A point of extreme interest, and one that has long been argued, concerns the individuality of the two gonadotrophic principles of the anterior pituitary. It was early established that an acid extract of the anterior pituitary contained a substance which primarily stimulated follicular growth whereas an alkaline extract acted more powerfully on the corpora lutea. This led to the belief that the gonadotrophic hormone in reality included two hormones. Investigators opposed to this view were of the opinion that the apparent difference in type of action was in reality a question of dose, a small amount of the hormone stimulating only the ripening of the follicle, a larger amount carrying the ovarian cycle through the phase of luteinization. Convincing chemical evidence, however, has accumulated in favor of the existence of two hormones. Fevold and Hisaw (1934) and Wallen-Lawrence (1934) have separated the two principles not only free from each other but also from the remainder of the pituitary hormones.

All the gonadotrophic principles thus far isolated from the anterior pituitary are protein in nature. Aside from the solubility characteristic of these proteins, little is known of their chemical properties.

Hyposecretion of Gonadotrophic Hormones. There is no clinical syndrome characterized by hyposecretion of gonadotrophic hormones alone. Thus in the two clinical conditions already described, pituitary dwarfism and pituitary cachexia, abnormal function of the sex glands can be attributed to the lack of the gonadotrophic principles. Also in this category is *dystrophia adiposogenitalis* or *Fröhlich's syndrome,* which is discussed at this point because the failure of development or regression of the sex glands constitutes a prominent feature of the disease.

Fröhlich's syndrome is usually associated with a chromophobic adenoma of the anterior pituitary gland, but it may also possibly result from simple hypofunction. Although many of the metabolic disturbances noted in this disease can be directly attributed to deficient secretion of the several pituitary hormones, it is also thought that pressure on the neighboring hypothalamic centers may contribute to the symptomatology. Fröhlich's syndrome can be recognized by the characteristic clinical triad of obesity, genital hypoplasia and faulty skeletal development. The distribution of fat is peculiar in that it is selectively deposited on the hips, lower abdomen and thighs. In the juvenile form of the disease the genitals and secondary sexual characteristics fail to develop. In the adult, the sex organs show retrogressive changes. The long bones in particular fail to grow in the young, and in males the skeletal structure is feminine in type. An increased glucose tolerance and a craving for sweets are also noted. Polyuria and polydypsia are frequent. Nervous and mental disturbances may be encountered due to pressure of the tumor.

Treatment. Hormonal therapy has yielded fair results in many cases of dystrophia adiposogenitalis. A combination of anterior pituitary extract and thyroid is particularly effective and dietary restriction is also helpful.

Hypersecretion of Gonadotrophic Hormones. Experimentally, gonadotrophic hormones can produce sexual maturity in immature animals. Presumably hypersecretion of the hormones in human beings would result in sexual precocity in young individuals and hyperactivity of the gonads in adults. The basophilic cells of the anterior hypophysis are believed to secrete the hormones. A clinical syndrome associated with basophilic adenoma of the anterior pituitary is known as pituitary basophilism or Cushing's disease (Cushing, 1932; *see* also review of Eisenhardt and Thompson, 1939). The more characteristic signs and symptoms of pituitary basophilism are striae of the skin, petechial and purpuric cutaneous lesions, acrocyanosis, adiposity, especially round the face, neck, trunk and abdomen, glycosuria, masculinization in the female, hypertension and osteoporosis. Many cases show definite indications of hypersecretion of the gonadotrophic principles. The disease in juveniles is characterized by sexual precociousness and premature puberty. In adults, however, the sex organs tend to atrophy. Adenomas of the adrenal cortex are frequently associated with pituitary basophilism and may cause many of the symptoms of the disease. This suggests that the adrenotrophic pituitary principle is liberated in excessive amount. The osteoporosis indicates that the parathyrotrophic substance is also secreted in excess. Irradiation of the pituitary results in remission of symptoms in a fair percentage of cases.

Anterior Pituitary-Like Gonadotrophic Hormones. In 1928, Ascheim and Zondek announced that during pregnancy large amounts of gonadotrophic hormones appeared in the urine and that this constituted a diagnostic test for pregnancy. The hormones could be detected by injecting pregnancy urine into immature mice and observing the ovarian responses consisting of follicular growth and luteinization. Naturally it was concluded that the source of these hormones was the anterior pituitary. Soon, however, reports of various investigators indicated fundamental differences between gonadotrophic substances isolated from the anterior pituitary and those from the urine of gravid females. To cite a few of these dissimilarities, there is a significant histological difference between the ovaries of young mice stimulated with gonadotrophic substances obtained from the anterior pituitary gland and those stimulated by the urinary gonadotrophic principles (Fluhmann, 1933) (Figure 111). The principles in pregnancy urine fail to stimulate the ovaries of hypophysectomized rats but the pituitary gonadotrophic principles are effective (Collip and associates, 1933). Also the urinary principles do not produce follicular development in monkeys (Diddle and Allen, 1933).

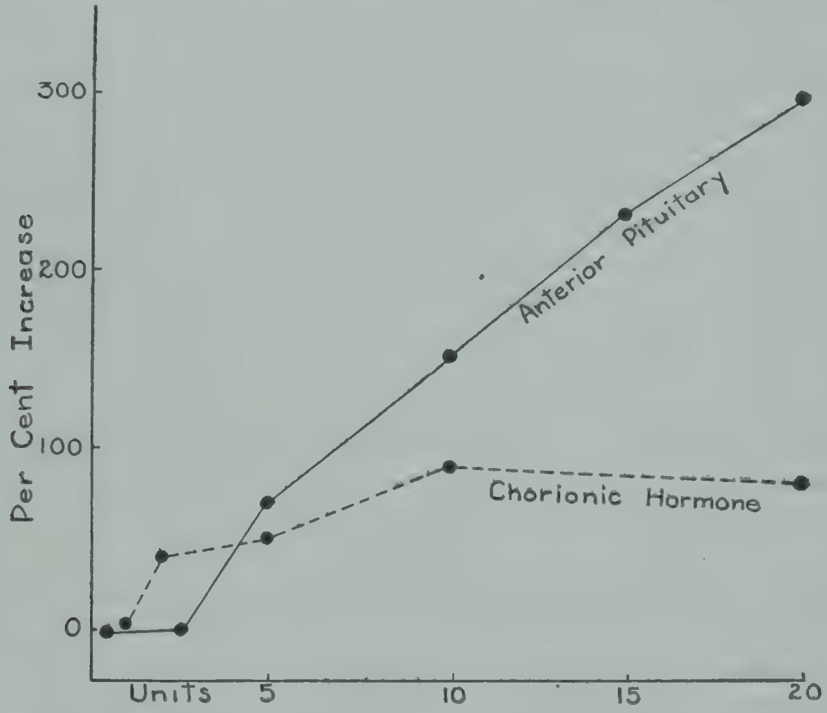

FIGURE 111. *The ineffectiveness of ascending doses of the chorionic gonadotrophic hormone (A.P.L.) in increasing the weight of the ovaries of immature rats as compared with the efficacy of anterior hypophyseal extracts.*

This is only one of several differences between the actions of the two types of preparations (see text). The "unit" employed in the experiment was the minimal dose capable of producing luteinization. (After Fluhmann, 1938. Courtesy of the *Association for Research in Nervous and Mental Disease.*)

It is now well established that the origin of the gonadotrophic substances found in pregnancy urine is the chorionic cells of the placenta. The same prin ciples are also excreted in the urine of individuals with hydatidiform moles, chorioepitheliomas and certain testicular tumors. What appears to be the true follicle-stimulating hormone of the anterior pituitary is found in the urine of women at the menopause and in the urine of castrates.

This difference is of practical importance because the gonadotrophic substances of both anterior pituitary and chorionic origins are marketed commercially and often little distinction is made between them. Indeed, the chorionic hormones are the active principles in the majority of available preparations. The particular point to be emphasized is that the hormones of chorionic and anterior pituitary origin are different in physiological activity, so much so that in primates the chorionic hormones produce hyalinization of ovarian follicles (Engle, 1933). There is no experimental evidence to show that the substances extracted from pregnancy urine alone can stimulate ovarian function in primates. The outstanding differences in physiological actions between the gonadotrophic hormones of the anterior pituitary and the substance found in the urine of pregnancy have been reviewed by the Council (1940).

Chemistry. The gonadotrophic hormone of the urine of pregnancy is probably a glycoprotein containing an acetylated hexosamine digalactose unit. The minimal molecular weight has been estimated to be between 60,000 and 80,000 (Gurin and coworkers, 1940).

Pregnant Mare Serum. Still another gonadotrophic hormone is obtainable from the serum of pregnant mares. This hormone is presumably of chorionic origin but its molecular size is such that it does not gain access to the urine. Pregnant mare serum in its physiological actions more closely resembles the gonadotrophic hormones of the anterior pituitary than it does the chorionic hormone of the urine of pregnancy. In contrast to the latter preparation, pregnant mare serum can maintain the ovary of the hypophysectomized rat and can stimulate follicular maturation in primates. Pregnant mare serum also appears to be a glycoprotein, containing a high percentage of carbohydrate. Its activity can be destroyed by acetylation of the amino groups, and in this manner it differs from the chorionic gonadotrophic hormone found in the pregnancy urine of humans (Li and coworkers, 1940).

Terminology. With three sources of so-called gonadotrophic hormones, terminology has become sadly confused. The confusion is largely due to the various trade names given to commercial products which give no hint as to the origin of the preparation. Synonymous terms for the gonadotrophic substance of placental origin are chorionic gonadotrophic hormone, anterior-pituitary-like (APL) hormone, pregnancy urine hormone (PUH) and prolan (a term formerly used to designate the pituitary gonadotrophic hormone). The gonadotrophic hormones of the anterior pituitary should be designated as the "pituitary gonadotrophic hormones" to avoid confusion. They are further differentiated as the follicle-stimulating hormone (FSH) and the luteinizing hormone (LH). Preparations obtained from the serum of pregnant mares are designated "pregnant mare serum."

Bio-assay. There are no official gonadotrophic hormone preparations, nor are any acceptable for inclusion in N.N.R. Consequently there is no prescribed method for the bio-assay of preparations and activity is expressed in terms of a variety of units. The pituitary and chorionic principles are usually assayed for their ability to produce follicles and corpora lutea in immature rats, one unit being defined as the amount necessary to produce the effect when administered in six divided doses over a period of three days. In the assay of certain preparations ovarian weight is used as an index; in others, the histological appearance of the ovaries is employed. It is probable, however, that the potency per unit of the different preparations is approximately the same.

In an attempt to lessen confusion in this field, the *Permanent Commission on Biological Standardization of the Health Organization of the League of Nations* has adopted an international unit for the chorionic gonadotrophic hormone. The unit is defined as the specific gonadotrophic activity of 0.1 mgm of a standard preparation. The standard is made up of a mixture of six preparations contributed by drug houses and is distributed upon request. The unit is to be used only to record activities of gonadotrophic principles of *human pregnancy urine*. The method of assay is not specified but the commission recommends that it be based upon changes in the gonads or secondary changes in the accessory reproductive organs of assay animals. The Council (1939) has adopted the international unit and the activity of any chorionic gonadotrophic preparation accepted for inclusion in N.N.R. must be expressed in international units.

Preparations. No preparation of gonadotrophic hormone is official. However, the Council has designated *Chorionic Gonadotropin* and *Follutein* as non-proprietary trade names for the gonadotrophic substance obtained from the urine of pregnant women and accepts products of this type conforming to Council regulations. The following preparations are available for hypodermic administration. *Gynantrin* (Searle) is an anterior pituitary preparation. It contains both FSH and LH. Whether this product is contaminated with other anterior pituitary hormones is not clear. It contains 100 rat units per cc. *Prephysin* (Chappel) is another anterior pituitary preparation but this product contains mostly FSH with only a trace of LH. Its strength is 25 rat units per cc. *Antophysin* (Winthrop) is a chorionic gonadotrophic principle obtained from pregnancy urine. It is marketed as a soluble powder in ampules containing 100 or 500 rat units. Tablets for oral administration containing 150 rat units are also available although it is extremely doubtful whether the principle has any activity by this route. *Antuitrin-S* (Parke, Davis) is not an anterior pituitary preparation as the name implies but contains the chorionic gonadotrophic principle of pregnancy urine. Its strength is 100 rat units per cc. *A.P.L.* (Ayerst, McKenna and Harrison) is a correctly named preparation containing chorionic gonadotrophic hormone isolated from the placenta. Each cc represents 100 or 500 international units. *Follutein* (Squibb), N.N.R., contains the chorionic gonadotrophic principle from pregnancy urine. It is marketed in a glycerin solution in vials containing 500, 1000 and 5000 international units. Provisions for dilution are supplied. *Gonadogen, Anteron* and *Gonadin* are proprietary names for preparations of pregnant mare serum.

Therapeutic Uses. The gonadotrophic hormones both of anterior pituitary and chorionic origin have been extensively employed in therapeutics in a wide variety of conditions. In many cases little rationale exists for the use of these preparations. Uncritical reports of successful therapeutic applications are abundant but experienced endocrinologists view these with scientific reserve.

Pituitary deficiencies such as *Fröhlich's syndrome* and *Simmonds' disease* have been treated with gonadotrophic hormones. Undoubtedly a deficiency in pituitary gonadotrophic principle is present and replacement therapy conceivably might be beneficial. There are two important points to keep in mind, however.

The diseases mentioned are characterized by a multiple pituitary deficiency and ideal treatment should include more than the gonadotrophic substances. Secondly, many reported cases have been treated with APL principles and there is no evidence that the chorionic gonadotrophic hormone of pregnancy urine can replace the anterior pituitary hormones in primates. If gonadotrophic hormones are employed in the treatment of these syndromes, the preparation should be of pituitary origin or possibly pregnant mare serum.

There is not a single clinical condition characterized by sexual hypofunction for which gonadotrophic preparations have not been recommended, tried and in many reports approved. Included in this group are genital hypoplasia, delayed puberty, amenorrhea, sterility and frigidity. The positive results are hard to reconcile with the known facts concerning the limitations in activity of the chorionic gonadotrophic preparations. There is insufficient evidence to state with any degree of certainty how these syndromes would respond to adequate therapy with gonadotrophic hormones of anterior pituitary origin. However, some results have been claimed for pregnant mare serum. For example, Huber and Davis (1940) have successfully treated the sterility resulting from anovulatory menstrual cycles with this type of preparation.

Functional uterine bleeding, especially that associated with hyperplasia of the endometrium, apparently responds to therapy with APL gonadotrophic principle. This has been confirmed by many investigators. Daily doses as high as 1000 international units have been employed.

Chorionic gonadotrophic hormone has also proved effective in the treatment of *cryptorchidism* and it is for the treatment of this condition that products are acceptable to the Council. As an experimental basis for this therapeutic procedure, Engle (1932) reported that the substance causes descent of the testes in immature monkeys. Success has occurred in a sufficient number of clinical cases to warrant hormonal therapy before surgical procedures are attempted. The dose commonly employed is 200 to 500 international units two or three times weekly. Treatment should be continued for no longer than one or two months in the absence of progressive descent. It is difficult to determine the value of gonadotrophic hormone in the treatment of cryptorchidism because some of the cases treated are probably pseudocryptorchidism, and the incidence of spontaneous descent is not known. In most instances following unsuccessful hormonal therapy, operation reveals a mechanical obstruction to the descent. Hormonal therapy appears to be of established value in distinguishing those cases which require surgical intervention, and it should be attempted before operative procedures are performed (*see* Rea, 1940).

Certain forms of intractable *dysmenorrhea* are said by some investigators to yield to therapy with the gonadotrophic hormones. However, the same claim has been made for many other hormonal preparations. It is difficult properly to evaluate therapy in this condition. The rationale for the use of gonadotrophic principle is to promote formation of luteal hormone. This in turn depresses excess muscular activity of the uterus which is believed to be one of the causes of symptoms. In most instances APL preparations have been employed. These might presumably be effective inasmuch as the pituitary gland is secreting an adequate amount of follicle-stimulating principle, and under such conditions the chorionic hormone is capable of carrying the ovarian cycle through the phase of luteinization. The daily injection of 200 to 500 international units is begun three or four days before the expected onset of menstruation and continued for one or two days after the flow has started.

Habitual abortion was formerly treated with gonadotrophic hormone on the basis that the failure of the uterus to retain its contents is often due to a deficient function of the corpus luteum. At present the luteal hormone, progesterone, is more often employed.

Acne vulgaris is believed by some to be the result of an endocrine disturbance. Successful therapy of this condition in boys and girls at the age of puberty with APL gonadotrophic hormone has been reported. A final statement on the value of this treatment must be reserved until more extensive evidence has accumulated.

PROLACTIN

Prolactin has been isolated in crystalline form free from other anterior pituitary constituents (White and collaborators, 1938). It is not available commercially and the therapeutic use of this principle has been limited to a few preliminary clinical trials.

Prolactin is necessary for normal lactation, being the third in the sequence of hormones involved in the normal function of the mammary gland. The development of the mammary gland which occurs during puberty is the result of the stimulating action of estrin. The hormone of the corpus luteum is responsible for the changes in the breast which occur during pregnancy. Finally the lactogenic hormone of the anterior pituitary is necessary for normal lactation following parturition. It is conceivable that lactation may fail because of a relative pituitary deficiency and prolactin might then prove of value in initiating the flow of milk. In a few isolated instances, this has been demonstrated to be true. Also lactation has been produced in hypophysectomized animals by substitution therapy with this hormone. Although rapid strides have been made in the physiology of the lactogenic hormone (Nelson, 1937), therapeutic contributions have been few, probably due to the fact that when lactation fails, bottle-feeding of the infant is easily employed and is more certain of success than pituitary replacement therapy in the mother.

THYROTROPHIC HORMONE

The thyrotrophic hormone, although a constituent of many anterior pituitary preparations, is not available to the physician in pure form. Therefore the therapeutic importance of this substance is not great. The thyrotrophic hormone may have clinical applications because thyroid deficiency characterizes several types of pituitary hypofunction and is often responsible for many of the outstanding symptoms.

Lack of the thyrotrophic hormone results in atrophy of the thyroid gland. This can be prevented or the atrophied gland can be restored to normal by the injection of pituitary extracts containing the thyrotrophic principle. The injection of the hormone into normal animals results in a marked hyperplasia of the thyroid. Accompanying this response there is an increase in basal metabolic rate and the symptoms of hyperthyroidism appear. With repeated injections, however, the response of the thyroid diminishes and the gland may show retrogressive changes.

ADRENOTROPHIC HORMONE

The existence of the adrenotrophic hormone is well established. In hypophysectomized animals, marked atrophy of the adrenal cortex occurs and this can be prevented by the administration of suitable anterior pituitary extracts. Also the adrenal cortex enlarges following the administration of active anterior pituitary extracts. Mention has already been made of the high incidence of adrenal tumors associated with pituitary basophilism. The possible relationship between the anterior pituitary, adrenal cortex and carbohydrate metabolism is discussed elsewhere (page 1218). There are no preparations of the adrenotrophic principle available for clinical use.

OTHER PRINCIPLES

The relations between the anterior pituitary, pancreas and carbohydrate metabolism are discussed in connection with the mechanism of action of insulin. The identity and specificity of the diabetogenic principle have yet to be established and one can only speculate on the clinical applications of such a substance. In the same category can be placed the ketogenic principle. Information concerning the parathyrotrophic and pancreatrophic principles is too meager to warrant a pharmacological discussion.

ANTIHORMONES

The concept of antihormones was introduced by Collip and Anderson (1934) who observed that rats receiving repeated injections of thyrotrophic hormone became refractory and eventually failed to respond to large doses. Furthermore, they observed that the serum of the refractory rats, when injected into non-refractory animals, apparently contained a substance which was capable of antagonizing thyrotrophic activity in the recipient animal just as effectively as it had in the donor. To this antagonistic substance Collip gave the name *antihormone*.

It requires little imagination to anticipate the wide therapeutic importance which antihormones might assume if future developments in this field uphold Collip's view that these substances are true antihormones and not merely immune bodies as many physiologists believe. Experiments designed to distinguish between these two possibilities have yielded conflicting results. In general, most of the evidence indicates that in species treated with hormone prepared from glands of that species, no refractoriness results; but, if extracts from one species are injected into heterologous species, an inhibitory substance which is not species-specific is obtained. Collip (1938), however, reported that sheep treated with a purified extract of sheep anterior pituitary produced an antihormone which inhibited in rats the gonadotrophic activity of hypophyseal hormone preparations obtained from bovine and pig glands as well as the extract originally employed.

It is chiefly to the protein hormones of the anterior pituitary that antihormones have been formed and this might be taken as evidence in favor of the immune body theory. Hartmann and associates (1938), however, have evidence of a rapidly acquired refractoriness to adrenal cortical extract injected into normal animals and this loss of response may be antihormonal in nature.

The evidence is presented merely to give some conception of the nature of the controversy concerning antihormones. The further development of this subject will be of great pharmacological interest for it may offer a therapeutic approach to glandular hyperfunction by the use of antihormones.

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CHAPTER 66

FEMALE SEX HORMONES

ESTROGENS AND LUTEAL HORMONE

Historical. It has long been known that the removal of the ovaries results in uterine atrophy and a loss of sexual functions. The hormonal nature of the ovarian control of the female reproductive system was established in 1900 by Knauer when he demonstrated that ovarian transplants functioned as effectively as did the organ *in situ*. This observation was extended by Halban (1900) who showed that even if the glands were transplanted from their abdominal site in immature animals, normal sexual development and function were assured. Thus the ovary was established as essential both for the growth and maintenance of the genital organs and seemingly it acted by secreting a hormone. The search for the active principle for a time proved futile because of the difficulty of assaying ovarian extracts. In 1923, Allen and Doisy devised a simple quantitative bio-assay method based upon changes produced in the vaginal smear of the rat. With this method it was soon discovered that an active principle was present in the blood and urine of pregnant females (Frank and associates, 1925; Zondek, 1928). The presence of large amounts of the estrogenic hormone in urine was a boon to the chemists who soon isolated this particular substance in crystalline form (Doisy and coworkers, 1929, 1930; Butenandt, 1929). A few years thereafter its chemical structure was elucidated.

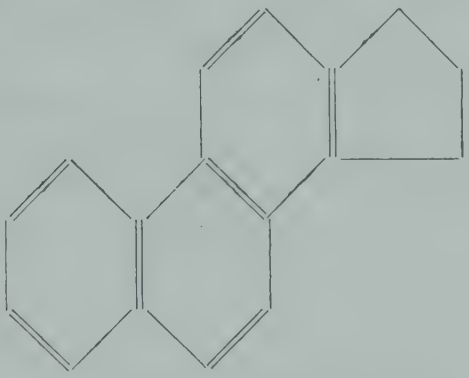
The important researches on the female sex hormone excreted into the urine during pregnancy obscured the discoveries of early investigations which indicated that the ovary secreted two substances. Beard (1897) had postulated on a purely theoretical basis that the corpus luteum served a necessary function during pregnancy. Born (1900) observed that the corpus luteum was absent from the ovaries of monotremes and suggested on this basis that it was required for the development of the placenta. Experimental evidence in support of this postulation was offered by Fraenkel (1903) who showed that destruction of the corpora lutea in pregnant rabbits caused abortion. It was not until the contributions of Corner and Allen (1929) that the hormonal function of the corpus luteum was firmly established. These investigators showed that the abortion which followed extirpation of the corpora lutea in pregnant rabbits could be prevented by the injection of luteal extracts but not follicular hormone.

Functions of the Female Sex Hormones. It is now established that two types of hormones are secreted by the ovary and the separate functions of each have been elucidated. One group is associated with the presence of developing or large Graafian follicles, the other with the corpus luteum. The follicular hormone is responsible for the development of the sex organs at puberty and for the secondary sex characteristics—such as the texture and distribution of the hair, the texture of the skin, the distribution of body fat, and the character of the voice—and their maintenance during adult life. The luteal hormone is necessary in the preparation and maintenance of the uterine endometrium for the normal implantation and nourishment of the embryo. It acts upon the mammary gland during pregnancy to prepare it for lactation. The luteal hormone suppresses further ovulation during pregnancy and keeps the uterus in a quiescent state. The follicular and luteal hormones are secreted in sequence under the influence of the rhythmic stimulation of the anterior pituitary, and their influence on the uterine endometrium accounts for the menstrual cycle. The pituitary gonadotrophic hormones have already been discussed.

FOLLICULAR HORMONE

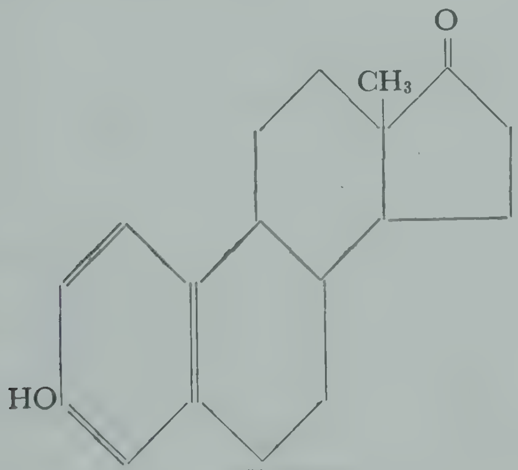
Terminology and Chemistry. The chemistry of the follicular hormone is complicated by the fact that the hormone is not an entity, but apparently exists in chemically related forms which differ in their activity. To the group of compounds having estrogenic activity has been given the name *estrogens*. The term estrogen, therefore, does not refer to a specific substance but rather to a group of compounds having particular actions in common. Even certain synthetic substances which possess similar biological activity but are not related chemically to the natural estrogens are included within this classification. As has already been stated, the first crystalline estrogen was isolated by Doisy and coworkers and by Butenandt. Doisy named his material *theelin* but other investigators failed to follow this nomenclature. Finally, in order to avoid confusion, the Committee on the Standardization of Sex Hormones of the League of Nations (1935) officially called the substance *estrone*. The Council on Pharmacy and Chemistry has accepted the terms estrone and theelin as non-proprietary synonyms.

All the estrogens of animal origin are chemically related derivatives of cyclopentenophenanthrene and have the following basic structure:



Cyclopentenophenanthrene

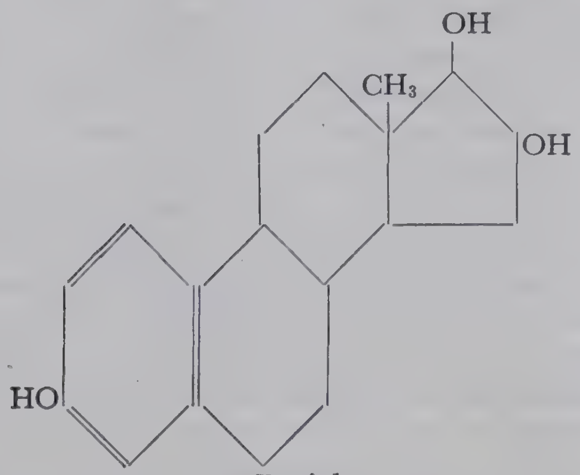
Estrone, or *theelin,* is a ketohydroxy derivative of cyclopentenophenanthrene and is sometimes called ketohydroxyestrin or ketohydroxyestratriene. It has the following structural formula:



Estrone

It is one of the most active of the estrogenic substances and is the standard of comparison for the activity of related compounds. Estrone is much more effective after parenteral than oral administration.

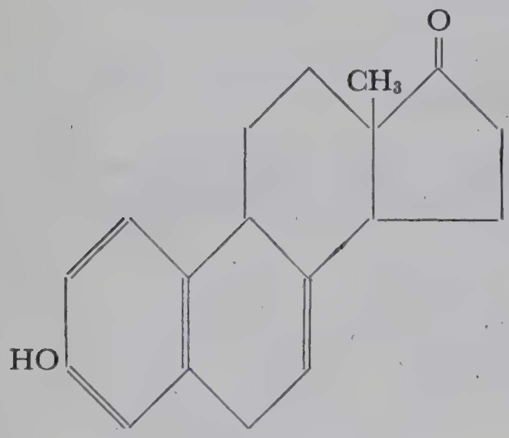
Estriol, or *theelol,* was isolated from urine independently by Doisy and associates and by Marrian in 1930. It was soon shown to be a hydrate of estrone with the following chemical structure. It is also called trihydroxyestrin.



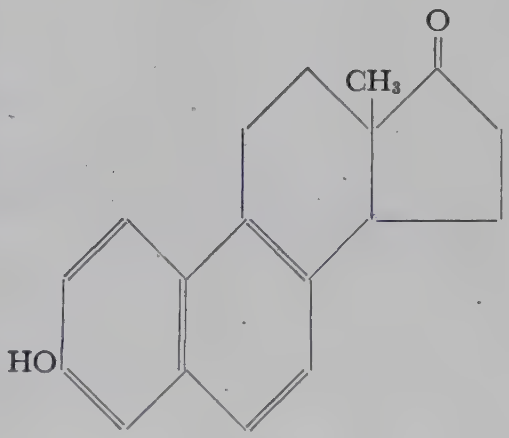
Estriol

Estriol is only about 1/10 as active as estrone but its action is somewhat more protracted. There is comparatively little difference between the effectiveness of this compound when given orally and parenterally, and therefore it allows the special advantage of oral therapy.

The next two estrogens to be isolated were obtained from the urine of mares late in pregnancy and called *equilin* and *equilenin* (Girard and coworkers, 1932). The former is about one-third and the latter 1/10 as active as estrone. Chemically they resemble estrone except that they are more unsaturated. These two compounds are not employed in therapeutics.

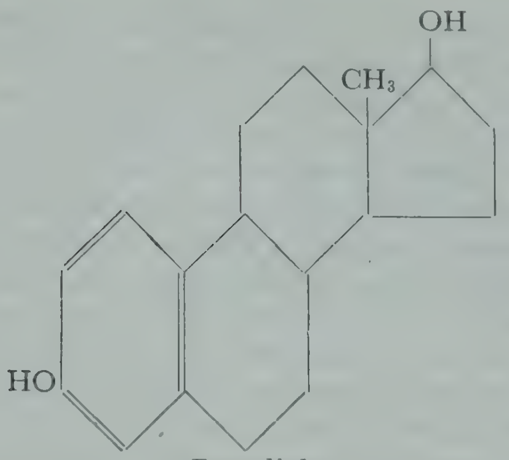


Equilin



Equilenin

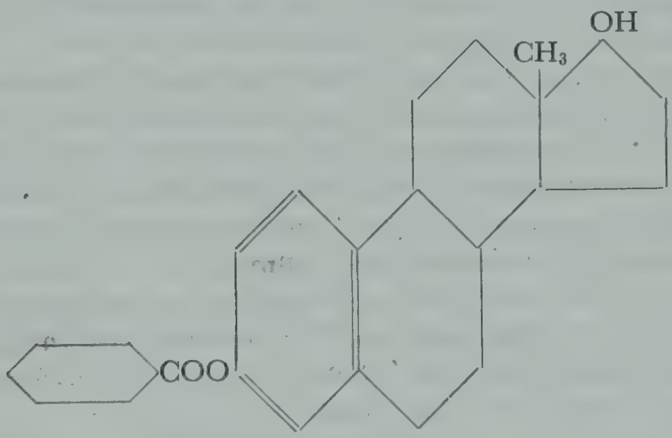
Estradiol was obtained for the first time by the reduction of estrone (Schwenk and Hildebrandt, 1933). The reduction product proved to be four to eight times as active as estrone. Chemically it may be termed dihydroxyestrin. The demonstration of the high activity of estradiol stimulated the search for this substance in the ovary, and it was isolated from that tissue by MacCorquodale, Thayer and Doisy (1935). It has also been identified in human pregnancy urine (Smith and coworkers, 1939). It is believed by some that the estrogenic hormone exists in the ovary in the form of estradiol and the substances obtained from other sources are secondary products. If this is so, the true ovarian hormone was synthesized and its chemical structure known before it was isolated from the gland which produces it. Estradiol is used in therapeutics. Its chemical structure is as follows:



Estradiol

It is interesting to note that if the two other ketohydroxy estrogens mentioned, equilin and equilenin, are reduced in a manner similar to estrone, the resulting dihydroxy compounds are also much more active than the parent substances.

A chemical advance that has proved valuable in the clinical use of the estrogens was the finding that esters of this group of compounds have a much more prolonged activity. Consequently the benzoic acid esters of estrone and estradiol are employed when a long-sustained action is desired. The following formula shows the chemical structure of estradiol benzoate:



Estradiol benzoate

The propionic acid ester of estradiol is also a valuable therapeutic agent with a long duration of activity.

Another estrogenic substance which is in the form of an ester is *emmenin*. This principle was isolated from the placenta by Collip and associates, 1934. Emmenin is a glycuronate of estriol (trihydroxyestrin). It is active orally and also has the sustained effect characteristic of the benzoic acid esters.

Various synthetic substances have been shown to possess estrogenic activity, some of them being more powerful in action than the naturally occurring estrogens. These are discussed separately at the end of this chapter.

Effects of High Concentrations of Estrogens. When a large amount of estrogenic substance gains access to the tissues it exerts effects quite distinct from any normal physiological action. These may be termed toxic reactions. Although most of them can be elicited only by the continued administration of large amounts of active material, it is important to keep these untoward effects in mind. The available estrogenic preparations are so potent and often given in such large doses that the possibility of toxicity is not too remote to be disregarded.

Estrogens *suppress pituitary activity* and when present in the body in large amount they inhibit the production of gonadotrophic hormone. That the secretion of other anterior pituitary principles is also diminished is evidenced by decreased growth in young animals and diminished thyroid activity. The effect on the thyroid is especially marked when that organ is hyperplastic. The inhibition of growth is associated with an early closure of the epiphyses. The practical significance of these observations is evident when one considers that the estrogens are extensively employed in the treatment of gonorrheal vaginitis in children. In such cases, dosage and duration of administration must be such as to preclude the possibility of permanently affecting future growth and development. High concentrations of estrogens also *inhibit the normal function of the ovaries and testes.* Both follicular development and spermatogenesis are retarded. The aforementioned effects have been demonstrated in human beings as well as experimental animals (Zondek, 1940).

The estrogens have a marked effect on *calcium metabolism.* It has been shown by Gardner and Pfeiffer (1938) that when high doses are given to mice and dogs there occurs calcification of the long bones, so extensive that there is almost complete disappearance of the marrow cavity. An associated secondary anemia develops. It is interesting to observe that whereas the long bones becomes hypercalcified, the pelvic bones lose calcium and become cystic. The basic mechanism of the calcium disturbance has not been determined, but these effects can be antagonized by androgens (Gardner and Pfeiffer, 1938). Zondek and Marx (1939) and Landauer and associates (1939) observed that the administration of estrogens to fowl causes an extreme degree of hypercalcemia and lipemia.

The administration of high concentrations of estrogens to animals causes *prostatic hypertrophy.* This action can be antagonized by androgens and it is largely on this basis that androgens have been employed clinically in the treatment of prostatic enlargement. The dose of estrogen necessary to affect the prostrate in experimental animals is high and there is no proof that prostatic hypertrophy in man is produced by a similar mechanism.

An observation of considerable interest is that estrogens can produce *uterine carcinoma* (Gardner and coworkers, 1938) in mice after huge amounts have been given over long periods of time. There is no clinical evidence of production of cancer associated with estrogenic therapy.

Large amounts of estrogen will cause *abortion* in pregnant animals, and the dose must be increased to produce this effect as pregnancy advances. Abortion induced early in pregnancy by estrogens probably results chiefly from endometrial changes which interfere with placental circulation, similar to those occurring after removal of the corpus luteum. Late in pregnancy, estrogenic-induced abortion is probably the result of increased uterine motility. As yet this action of the estrogens has had little therapeutic application.

Absorption and Excretion. All the estrogenic substances can be absorbed when given by mouth. The discrepancy between the effective parenteral and oral doses of estrone is greater than that of estriol. This is probably not related to the ease of gastro-intestinal absorption for there is evidence that estrone readily gains access to the body through the intestinal mucosa (Kemp and Pedersen-Bjergaard, 1937). After oral administration, however, estrone is rapidly eliminated by the kidneys, the excretion being almost over in 24 hours and complete in 48 hours. About three to ten per cent of orally administered estrone is excreted into the urine, as determined by the increase in estrogenic activity of the urine. There is no proof that estrone is excreted in as active a form as that administered. It may be changed to a much less potent estrogen and the apparent 90 per cent destruction in the body may represent no more than a slight change in the configuration of the molecule. This decomposition is believed to take place in the blood and liver.

There is evidence that endogenous estradiol is converted in the body to estrone. This in turn is believed to be changed in part to estriol under the influence of progesterone. It has been suggested that the onset of menstruation and the initiation of labor may be due to a fall in concentration of progesterone. As a result, estrone is not converted to estriol and accumulates in the body tissues (Smith, Smith and Pincus, 1938).

After oral administration of the estrogens, the rapid absorption and excretion result in a very poor physiological response. Seemingly the blood concentration rises and falls sharply and consequently the duration of action is short. Therefore, when oral therapy with the estrogens is employed, small and frequent doses should be given. A more favorable response is obtained from the parenteral administration of estrogens in oil. Absorption is greatly retarded and duration of action is therefore lengthened. The maximal duration of action is obtained from the benzoic and propionic acid esters of the estrogens given hypodermically in oily solution. The relative efficiency of the oral and hypodermic routes of administration cannot be stated with certainty; but, as an approximation, five times the parenteral dose should be prescribed for oral medication.

The estrogens can also be absorbed from other mucous membranes. The use of vaginal suppositories results in a favorable response, especially if one is desirous of producing histological changes in the vaginal mucosa. In this instance, estrogens seemingly gain direct access to the mucosal cells, for by direct application the dose can be reduced to a minimum. Estrogens can also gain access to the circulation through the skin if applied in a suitable fatty vehicle. Ointments containing estrogens for application by inunction are available.

Estrogens, in common with other crystalline endocrine preparations, are slowly absorbed if pellets of crystalline hormone are implanted subcutaneously. In some types of hormonal therapy, this procedure is desirable inasmuch as a slow, even rate of absorption is assured and chronic medication is facilitated. However, Walter and coworkers (1940) have demonstrated that when estradiol or estradiol benzoate is implanted in this manner, the pellets soon become encased in a fibrous capsule and the absorption of the hormone in effective amounts ceases at a time when only a relatively small amount of the pellet has been absorbed.

Bio-assay and Unitage. The activity of estrogenic substance is bio-assayed in rats by the method of Allen and Doisy previously mentioned. One *international unit* represents the estrogenic activity of one-tenth microgram (0.0001 mgm) of crystalline estrone. It is unnecessary to assay crystalline estrogenic substances and the doses of crystalline estrone, estriol and estradiol should be prescribed in terms of weight rather than units. The activity of concentrates prepared from urine or placenta must still be expressed in units. Unfortunately in the assay of many commercial preparations, the older Allen-Doisy rat unit, which is from three to 20 times (depending on the compound and method of assay) as potent as the current international unit, is still employed. If one remembers the relationship between the international unit, the Allen-Doisy unit and crystalline estrone, the comparative therapeutic value of most of the available preparations can be approximated.

Preparations. The available pharmaceutical preparations of estrogenic substances can be divided into three main groups. One type of preparation of naturally occurring estrogens is made from pure crystalline compounds of known chemical composition and potency, and the dose is prescribed by weight rather than units. Another type of preparation represents a purified concentrate of natural estrogen prepared from some potent source material. The activity is determined by bio-assay and the dose is prescribed in units. Finally there are crystalline preparations of synthetic estrogens. Following is a list of several of the available natural preparations (for complete list, *see* Pratt, 1939):

Theelin (Estrone), N.N.R., Parke, Davis and Co. This is a crystalline product obtained from the urine of pregnancy.
Theelol (Estriol), N.N.R., Parke, Davis and Co. This is a crystalline product obtained from the urine of pregnancy.
Progynon-DH. Schering. This is crystalline estradiol.
Progynon-B. Schering. This is crystalline estradiol-benzoate.
Amniotin, N.N.R., Squibb. This is a bio-assayed concentrate of estrone obtained from the urine of pregnant mares.
Emmenin. Ayerst, McKenna and Harrison. This is a bio-assayed placental extract for oral use, probably containing mainly an ester of estriol.

Many of the preparations listed are available in several forms, allowing for administration by any desired route. Thus there are capsules and tablets for oral administration, ampules of aqueous or oily solutions for injection, suppositories for vaginal use and ointments for inunction. Also drug concentrations are varied to permit a wide range in dosage.

Therapeutic Uses. The estrogenic substances have a variety of therapeutic uses. Some of these have a definite physiological basis and are well established; others are more in the nature of empirical applications.

At the time of the *menopause,* there is a readjustment in the hormonal balance of the body. The ovaries gradually cease functioning and the follicular and luteal principles are no longer formed. In response to this deficiency there is a compensatory hyperfunction of the anterior pituitary and large amounts of gonadotrophic hormone can be detected in the urine. Many symptoms often accompany the menopause. Some of these are undoubtedly psychic in origin but others are unquestionably organic. It is the latter group which responds to substitution therapy with estrogenic principles. Menopausal vasomotor disturbances and migraine can often be relieved. No set rules of therapy can be applied and dose, route and duration of medication must be adjusted to the individual case. The oral ingestion of estrone in the dose of 0.06 to 0.12 mgm one to four times daily may be sufficient to control symptoms. On the other hand, it may be necessary to resort to parenteral injections of as high as 50,000 international units (five mgm) of estrone. Dosage should be reduced at frequent intervals in order to determine whether it is possible to terminate treatment. A common procedure is to start with the parenteral administration of 10,000 units of a suitable estrogenic preparation in order to control immediate symptoms. The dose is then adjusted in order to meet individual requirements. At the termination of therapy, the hormone should be withdrawn gradually rather than abruptly.

On the theory that many symptoms of the menopause result from hyperactivity of the anterior pituitary, some clinicians have advocated irradiation of this gland in preference to hormonal therapy. Novak (1938) is of the opinion that hormonal therapy is the procedure of choice to be followed by mild irradiation if estrogenic principles fail to give relief.

Gonorrheal vaginitis in children is another condition which yields to therapy with estrogenic substances. The rationale of this treatment is to change the immature vaginal mucous membrane to the adult type. This morphological transition is accompanied by a marked acidification of the vaginal secretions and Lewis and Weinstein (1936) believe this to be the chief factor in eradicating the organism. When the therapy was first introduced, large amounts of estrogenic substances were administered by injection. It has since been found that local application is not only more effective but reduces the dose required and therefore the incidence of undesired side-actions. Suppositories containing 1000 to 2000 units of an estrogen are inserted into the vagina nightly until the infection is controlled. It may be necessary in severe cases to supplement local therapy with hypodermic injections. Swelling of the breasts, slight growth of pubic hair and some uterine bleeding may accompany treatment but these effects subside as soon as the hormone is withdrawn. Therapy is expensive and this is an important consideration especially because many of these patients are indigent. It is therefore of interest that sulfanilamide and sulfapyridine promise to be effective and offer an alternative therapy for this most troublesome disease.

Estrogens have also proved to be of value in the treatment of *senile vaginitis.* The basis of therapeutic action is again the histological changes induced in the vaginal mucosa. Local therapy with estrogen-containing suppositories is most efficacious.

The empirical use of a single hormonal preparation for the treatment of *amenorrhea* does not take into account the many factors involved in normal menstruation, the failure of any one of which may suppress menses. Frank and coworkers (1937) carefully studied amenorrheic women and found wide variations in the blood and urine concentrations of estrogenic and gonadotrophic principles. Therapy with estrogens gave poor results and it was concluded that this type of hormone was not useful for the treatment of amenorrhea. The judicious and successive administration of hormones of the Graafian follicle and corpus luteum may produce uterine bleeding but aside from the psychic benefit that a menstrual period may give to the patient, little else has been accomplished. This therapy is very costly.

Estrogens have been employed for the treatment of *menorrhagia* and *metrorrhagia.* These symptoms may result from a variety of causes, and there is no justification for endocrine therapy unless careful clinical and laboratory examinations demonstrate a specific hormonal cause for abnormal bleeding. If used routinely, the results are bound to be disappointing for only a small percentage of cases respond favorably.

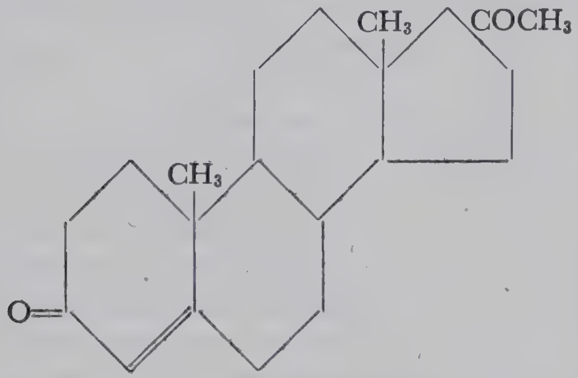
Dysmenorrhea has been treated with various types of hormonal preparations. There seems little rationale for the use of estrogenic substances, especially if one accepts the view that pain results from excessive uterine motility and that estrogens stimulate motor activity of the uterus.

Frigidity has been treated with estrogenic substances and favorable results have been reported. There is some rationale for this type of therapy in certain cases, but it is extremely difficult properly to evaluate the results obtained. There is little reason for the recommended treatment of *sterility* with estrogens. It has been claimed that the hormones promote a type of vaginal secretion more favorable for spermatozoa, but this is a questionable effect on only one possible cause of sterility. If sterility is the result of a failure of ovulation, there is no reason to believe that estrogenic therapy would be of value.

Favorable results have been reported in the treatment of *acne vulgaris* with estrogens. Therapy is based upon the finding that the high incidence of the skin disorder during puberty is associated with a low production of estrogen. Further study must be awaited before this type of treatment can be considered valid. The use of estrogenic principles in the treatment of *hemophilia* has been advocated, but the clinical results have been disappointing.

LUTEAL HORMONE

Terminology and Chemistry. Following the convincing demonstration by Corner and Allen of the presence of a hormone in the corpus luteum, chemists were unrelenting in their efforts to isolate the active material and establish its chemical structure. This was accomplished independently by four groups of investigators in 1934 and the active principle was named *progesterone.* Corner and Allen in their earlier publications had called the luteal hormone *progestin,* but this term is now used generically in the same manner as estrogen. Progesterone occurs in two polymorphic forms which differ only with respect to their melting points and crystalline structures. Biologically they are identical and although they are designated as alpha and beta progesterone, for practical purposes they are the same substance. The structure of progesterone is as follows:



Progesterone

The chemical relationship of the luteal principle to the estrogens and androgens is at once apparent. It has been pointed out, however, that a large group of substances possess estrogenic activity. Likewise substances chemically related to the male hormone share its physiological effects. It is of interest, therefore, that although many compounds closely related to progesterone have been formed, none of these has all the characteristic physiological activities of the luteal hormone.

The yield of progesterone from ovaries is low and therapy would be prohibitive in cost if one had to rely upon this source. Fortunately, the hormone has been synthesized from chemically related but more available substances and it is this synthetic material which is now marketed for therapeutic use.

Absorption, Fate and Excretion. Progesterone is effective only after parenteral administration. It is not known whether the lack of response after oral ingestion is due to destruction or the failure of absorption from the intestine. The hormone is usually injected intramuscularly in an oily vehicle. Absorption is apparently slow because good clinical results have been obtained from single weekly injections.

Both endogenous and injected progesterone is excreted into the urine largely in the form of *pregnanediol,* a compound chemically related to progesterone, but physiologically inactive. The estimation of the amount of pregnanediol in the urine has been used as a means of ascertaining the rate of production of progesterone in the body. It has been observed that pregnanediol is found in the urine only during the luteal phase of the menstrual cycle. During the first two months of pregnancy the concentration of pregnanediol in the urine is approximately the same as during the menses. It then rises progressively until a peak is reached at the eighth month. Within 24 hours postpartum, the urine is free of pregnanediol.

There is evidence that the conversion of progesterone to pregnanediol takes place in the uterus (Venning and Browne, 1937; Browne, Henry and Venning, 1938).

Preparations and Bio-assay. Crystalline synthetic progesterone is available for therapeutic use. It is prescribed by weight rather than by units. There are also active extracts containing progesterone obtained from placenta. These are assayed by the Corner-Allen technic. Female rabbits are mated and then castrated. Preparations to be assayed are injected in five equal daily doses, and the response of the uterus, compared with that obtained after crystalline progesterone, determines the degree of activity. Another technic employs immature rabbits and the uterus is first prepared by the injection of an estrogen after which the solution containing the luteal principle is assayed. One international unit is the equivalent of one mgm of beta-progesterone.

Therapeutic Uses. A valuable therapeutic use of progesterone is in the treatment of *habitual abortion*. The mechanism of action is apparently the suppression of uterine motility to prevent premature expulsion of the contents. It is possible that in the earlier stages of gestation progesterone acts to maintain a proper type of endometrium and to insure an adequate circulation to the fetus. Rules for dosage are not yet established. Kane (1936), in a series of 40 cases, injected 1/25 of an international unit (40 γ) of progesterone every other day for ten doses and repeated this course of injections at intervals of three weeks up to the thirty-second week of pregnancy. His results were quite successful. Elden (1938), in another series of cases successfully treated, administered one unit weekly until about the sixth month of pregnancy. He gave additional hormone when the circumstances seemed to demand but states that smaller amounts may be sufficient to carry the pregnancy to term. Campbell and Sevringhaus (1940) also obtained excellent results with the injection of one to two rabbit units weekly. However, MacGregor and Stewart (1939) emphasize that large amounts of progesterone are normally secreted during pregnancy, a fact which they find hard to reconcile with the success attained in the treatment of habitual abortion with small doses of progesterone. They find it necessary to inject as much as 10 or 20 mgm of progesterone twice weekly in some cases and attribute many of their failures to small dosage (one mgm twice weekly).

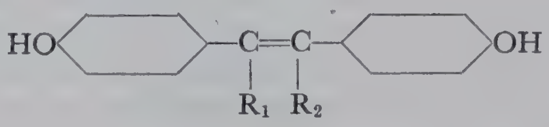
It is interesting to note in connection with the treatment of habitual abortion with progesterone that Kane observed a high incidence of fetal malformations, probably indicative of abnormal ova or defective decidual reactions. It has been suggested that such malformations may be the basis for certain cases of habitual abortion.

Progesterone has been used in the treatment of *amenorrhea*. It is usually employed in conjunction with estrogens. Although this combination therapy may be successful in producing uterine bleeding, its ultimate value can be seriously questioned.

Progesterone has been advantageously employed in the treatment of *afterpains* following parturition. It is also said to relieve *dysmenorrhea*. In both conditions, the mechanism of action of progesterone is probably to reduce the motor activity of the uterus.

SYNTHETIC ESTROGENS

A number of synthetic compounds, of less complicated structure than the naturally occurring estrogens or their closely allied chemical derivatives in that they do not possess a cyclopentenophenanthrene nucleus, have been shown to possess estrogenic activity. Most notable of the group are the derivatives of diphenylethylene (stilbene). Dodds and coworkers (1938) studied the relationship between chemical structure and pharmacological activity of many of these substances. The most interesting results were obtained with a series of compounds in which alkyl groups were substituted in the basic structure 4,4′-dihydroxystilbene, a compound having the following structural formula in which R_1 and R_2 represent the sites of substitution:



In Table 59 are shown the effects on estrogenic activity of various substitutions in the above structure. The greatest activity is shown by the compound in which two ethyl groups have been substituted (4,4′-dihydroxy-alpha-beta-diethylstilbene). To the compound, because of its origin and high estrogenic activity, has been given the name stilbestrol (diethylstilbestrol).

TABLE 59

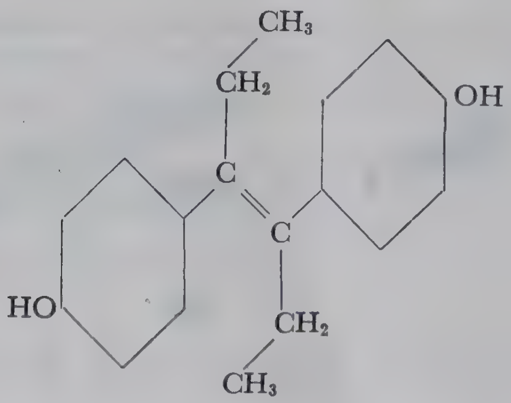
ESTROGENIC ACTIVITY OF DERIVATIVES OF DIHYDROXYSTILBENE

R_1	R_2	UNITS* OF ESTROGENIC ACTIVITY PER GRAM
H	H	140
H	C_2H_5	5000
CH_3	CH_3	40,000
CH_3	C_2H_5	1,000,000
C_2H_5	C_2H_5	3,000,000
C_2H_5	nC_3H_7	300,000
nC_3H_7	nC_3H_7	50,000
nC_4H_9	nC_4H_9	5000

* By the method of assay employed estrone possesses an activity of 700,000 units per gram.
Dodds and coworkers (1938).

Stilbestrol

Chemistry. As has already been stated, stilbestrol differs sharply from estrogens occurring naturally in that it does not possess a cyclopentenophenanthrene nucleus. However, as Dodds pointed out, the structure of the compound is not far removed from that of the cyclopentenophenanthrene derivatives, as can be seen when the structural formula for stilbestrol is written in the following manner:



It is therefore highly probable that a common type of structure is responsible for the pharmacological activity of both the natural and synthetic estrogens. It is also obvious from the data presented in Table 59 that the alkyl groups substituted in the R_1 and R_2 positions of the skeleton structure are of primary importance from the point of view of pharmacological activity. This finding may possibly be extended to indicate essential features in the relation between pharmacological activity and chemical structure of the natural estrogens.

Pharmacological Actions. The actions of stilbestrol are almost identical with those of the natural estrogens. Both the physiological and pathological changes which can be effected by estrone and related compounds can be duplicated by stilbestrol. With respect to activity, stilbestrol is many times more potent than estrone when administered orally, and about two to four times as active when given parenterally. It is less active than estradiol, however, after parenteral administration.

Toxicity. There is little doubt that stilbestrol is more toxic than the naturally occurring estrogens. Most of the information on the toxicity of the compound has been obtained from clinical studies and opinions do not agree. The most unfavorable report with respect to toxicity is that of Shorr and coworkers (1939). In a series of 44 cases, 80 per cent of the patients showed untoward symptoms. These most commonly took the form of gastro-intestinal disturbance and consisted of nausea, vomiting, anorexia, abdominal distress and diarrhea. Seventy-two per cent of the subects complained of lethargy. Eight patients showed cutaneous rashes, two experienced paresthesia, one noted marked thirst and one exhibited a psychotic episode. So alarming were the reactions that Shorr and associates were forced to conclude that stilbestrol in its present form is not suitable for use in human beings and the experimental development of the drug should be confined solely to experienced endocrinologists.

In contrast, other investigators report fewer untoward effects from the use of the compound. Although nausea and vomiting have been noted in almost every extended study of the drug, the incidence has not been high. Buxton and Engle (1939) report gastro-intestinal disturbance in 23 per cent of a series of 17 patients and record one case in which albumin and casts appeared in the urine. MacBride and coworkers (1939) observed nausea in 21 per cent and vomiting in nine per cent of a series of 37 patients. In a subsequent series of 56 cases the incidence of unpleasant effects was only 16 per cent (McBryde and coworkers, 1940). Other investigators report a still lower incidence of untoward effects (*see* discussion of Shorr and coworkers, 1939).

No explanation is readily available to account for the divergent results. Shorr and coworkers and Buxton and Engle found no relationship between dosage and untoward effects. The doses that Shorr and associates employed varied and were determined by the amount necessary to produce a desired therapeutic result. They believe that an attempt to lower the incidence of unpleasant reactions by a reduction of dosage would not allow a proper therapeutic evaluation of stilbestrol. It is also evident from the studies of Shorr that the gastro-intestinal distress does not result from a local action of stilbestrol inasmuch as it is just as evident after parenteral administration.

Absorption, Fate and Excretion. Stilbestrol is readily absorbed after oral and parenteral administration. The drug is apparently not inactivated in the gastro-intestinal tract and hepatic circulation for the compound loses only approximately 50 per cent of its activity after oral administration. From this point of view, stilbestrol is one of the most desirable of the estrogens for oral therapy.

Esterification of stilbestrol increases the duration of action upon subcutaneous but not upon oral administration (Emmens, 1939).

The fate of the drug in the body is unknown. Whether it is converted to a cyclopentenophenanthrene derivative cannot be stated.

Preparations. Stilbestrol has no official status and is not included in N.N.R. The drug is at present available only for experimental purposes. Its dose by the oral route is approximately two to four mgm, but this may be greatly varied in individual cases.

Therapeutic Uses. The therapeutic indications for stilbestrol are the same as those for natural estrogens and the compound has been used successfully in the treatment of many of the conditions requiring estrogenic therapy. Relatively few clinical reports have appeared, however, and judgment as to the ultimate value of the drug must be reserved. The compound is seemingly very effective in the control of menopausal symptoms and can conveniently be given by mouth. The dose varies from patient to patient, but the majority are relieved by amounts of from one to five mgm daily (*see* Davis, 1940; Huberman and Colmer, 1940; Weed, 1940; Kurzrok and coworkers, 1940). Stilbestrol has also been successfully employed in the treatment of prepuberal gonorrheal vulvovaginitis (Russ and Collins, 1940). The drug was given orally in the dose of one mgm three times daily for 20 doses. Enlargement of the breasts and vulva may be noted, but regression occurs after the drug is discontinued.

Stilbestrol is much cheaper than other estrogens, and is highly effective by mouth. These are the main advantages of the drug over the natural estrogens, but stilbestrol must be demonstrated to be relatively non-toxic before the factors of cost and ease of administration can be permitted to determine the choice of preparation.

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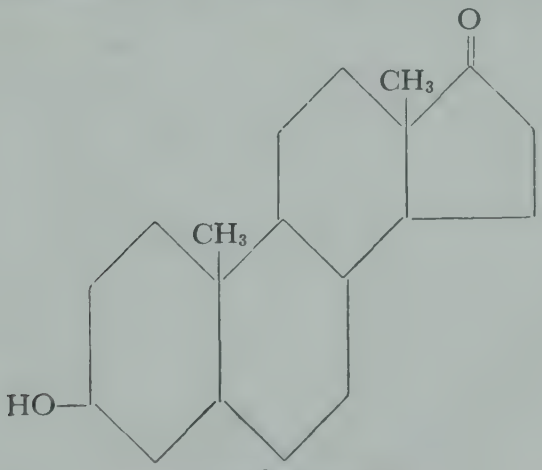
CHAPTER 67

MALE SEX HORMONES

Historical. The relation between the testes and secondary sex characteristics of the male has long been known. Indeed the fact that the testes were glands of internal secretion was demonstrated as early as 1849 by Berthold who showed that the transplantation of gonads into castrated roosters prevented the typical signs of castration. This was the first experimental demonstration of hormonal action of any type. However, it was not this observation but rather the popular belief that failure of testicular function was the cause of the symptoms of old age in men that stimulated many attempts to isolate an active testicular principle. As an example of the wide acceptance of this belief may be cited the experiments of Brown-Séquard (1889), one of the foremost physiologists of his time, who prepared testicular extracts and administered them to himself. He was convinced that he had gained in vigor and capacity for work from the treatment.

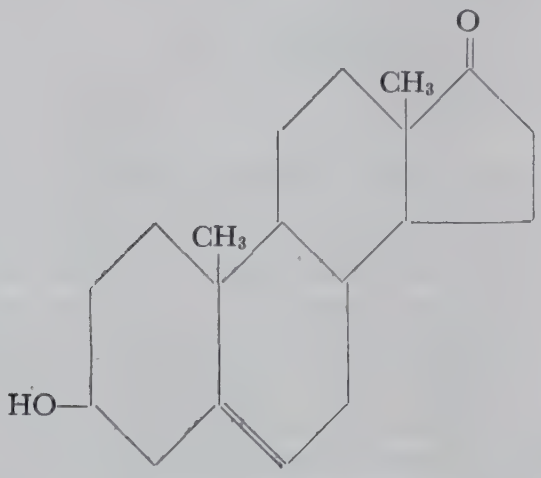
It is only within recent years that active preparations of the testicular hormone have become available and therefore most of our early knowledge of the function of the male gonads was obtained from extirpation experiments. These have given valuable information which is now being supplemented by clinical studies on the effects of injection of the active principle of the testicle.

Chemistry and Terminology. The elucidation of the chemistry of the male sex hormones was greatly stimulated by the development of methods of assay. The procedure of Koch and coworkers for the determination of androgenic activity, which utilized the long-known growth response of the capon's comb, was the necessary tool which enabled the chemist to isolate the active principle in crystalline form. This isolation was first accomplished by Butenandt (1931) who by Herculean effort obtained 15 mgm of crystalline material from 15,000 liters of male urine. The urinary principle was called *androsterone* and in 1932, with only 25 mgm of available material, Butenandt proposed a structural formula which was later shown by synthesis to be correct (Ruzicka and coworkers, 1934).



Androsterone

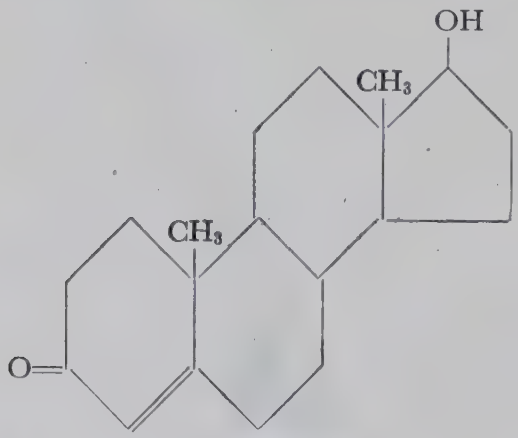
Further chemical investigations led to the isolation in 1934 by Butenandt and Dannenbaum of another androgenic principle from urine which differed chemically from androsterone in being more unsaturated. This was termed *dehydroisoandrosterone.*



Dehydroisoandrosterone

Studies of chemical derivatives of these substances yielded further information. Thus, it was observed that the esterification of androsterone with acetic acid led to the formation of androsterone acetate which was as potent as the original material but had a greatly prolonged duration of action. Also, the reduction of androsterone to the compound *androstanediol* increased activity two to three times in much the same manner as does the reduction of estrone to estradiol. These are only two of the many chemical similarities between the male and female sex hormones. Inspection of the respective formulas clearly shows their close structural relationship. The main difference, aside from the presence of an extra methyl group, is the degree of saturation. Indeed, it is possible to prepare unsaturated derivatives of androsterone more closely approximating estrone in structure which possess both androgenic and estrogenic properties.

Attention was also focused on the testes as a source of male sex hormone for it was desired to determine whether the active substance obtained from the urine was identical with that formed by the gland. It was soon evident that marked physiological and chemical differences existed between the extracts of testicle and androsterone. For example, active testicular extracts which were equal to androsterone in their ability to promote comb growth in capons had a much greater effect on the seminal vesicles of castrate rats. The testicular principle was isolated in crystalline form by David and associates (1935) and soon its chemical structure was elucidated. This substance was called *testosterone.*



Testosterone

Testosterone is ten times as active as androsterone in promoting comb growth in the capon. Furthermore, one capon unit of testosterone is seven times as potent as one capon unit of androsterone in its action on the seminal vesicles of castrate rats. In all probability, testosterone is the true testicular hormone, and the urinary androgenic substances are thought to be derived from it by chemical changes in the body. One might say, therefore, that androsterone and dehydroisoandrosterone bear the same relationship to testosterone as do estrone and estriol to estradiol. The group of male sex hormones collectively is known as androgens.

Physiological Functions. The male sex hormone has a variety of functions. It is probable that even *in utero* the maternal anterior pituitary excites the fetal gonads to secrete androgenic substance and this in turn may be responsible for the prenatal stimulation of some secondary sexual characteristics and for the descent of the testes. Male sex hormone has been identified in the testes of fetal cattle but it disappears shortly after birth. At the time of puberty, as a result of stimulation by the anterior pituitary, the permanent phase of testicular activity is initiated. The secreted androgen is necessary for the development of the sex organs and the secondary sex characteristics of the male. During adult life not only are the androgens necessary for the maintenance of the sex characteristics but also for the integrity of the seminal vesicles, prostate, epididymis and Cowper's gland. The testicular hormone can maintain spermatogenesis in some species of hypophysectomized animals, and thus may be related in some manner to this function.

Effects of Castration. The effects of castration in man depend upon whether loss of testicular function occurs before or after adolescence.

Prepuberal Castration. The loss of the testes before puberty or their failure to function properly precludes the possibility of normal growth or sexual development. In an individual so afflicted, the penis remains infantile, secondary sex characteristics fail to appear and growth is abnormal in that ossification of the epiphyses of the long bones is retarded and the limbs are thus disproportionately long in comparison with the trunk. Obesity is common and the distribution of fat tends to resemble the feminine type.

Postpuberal Castration. It is difficult to obtain a clear picture of the postpuberal castrate. The signs and symptoms of this deficient state have not been carefully recorded and the literature contains contradictory statements as to the appearance, symptoms and behavior of postpuberal castrates. The following outstanding features of the syndrome have been described by Hamilton (1939) who made an extensive study of a large number of castrates in connection with the effects of replacement therapy. After castration, the complexion usually becomes pale and pasty. This is not due to anemia. Blood flow, at least in the skin, is diminished and many castrates have a definite hypotension (Edward, Hamilton and Duntley, 1939). It is almost impossible for the castrate to tan after exposure to ultraviolet rays; but, subsequent to exposure, typical pigmentation of the skin can be brought out by the administration of androgens (Hamilton and Hubert, 1938; Hamilton, 1939).

The following changes gradually occur over a period of years. The beard regresses and becomes so light that there is little necessity for shaving. Also the axillary and pubic hair becomes sparse and silky and there is a loss of hair on the arms and legs. The voice elevates in pitch but remains masculine in type and does not resemble that of the prepuberal castrate. The change in voice occurs so slowly that it may not be noticed by the patient until replacement therapy effects a sudden return to the normal timbre. Muscular changes occur and are characterized chiefly by a muscle flabbiness and diminished size and strength. The face loses its normal deep lines and muscular development, the chest muscles are poorly defined, and the musculature of the limbs changes to give the extremities a feminine appearance. A high percentage of patients tend to become obese and distribution of fat is largely around the mammary region, abdomen and mons pubis. The external genitalia atrophy but never reach that stage of underdevelopment characteristic of the prepuberal castrate. The penis, scrotum, circumanal region and areolar areas lack their usual pigmentation. The patients commonly complain of weakness, listlessness, lack of endurance and loss of libido and potentia. An interesting symptom is the occurrence of frequent episodes of vasomotor disturbances characterized by hot flushes and sweating similar to those experienced by women at the time of the menopause. The effects of replacement therapy will be discussed.

Pharmacological Actions. *Effects on Sex Organs and Secondary Sexual Characteristics.* The outstanding actions of the androgens on the sex organs and secondary sexual characteristics can readily be demonstrated in hypogonadal subjects or in individuals before the age of puberty. For example, the injection of androgen in immature boys causes erection of the penis which may approach a state of priapism (Hamilton, 1937). Continued administration in cases of hypogonadism causes growth of the sex organs and development of secondary sexual characteristics. In this regard, the androgens are most effective when administered at a time near the normal age of puberty. The longer the duration of gonadal deficiency, the less is the likelihood that replacement therapy with androgens will prove effective.

Androgens, like estrogens, inhibit the activity of the anterior pituitary and gonads. If a high concentration of androgen is maintained in the circulation by injection, the secretion of the gonadotrophic and possibly other principles of the anterior pituitary is diminished. Spermatogenesis is retarded and may even be suppressed completely. These actions give rise to certain problems in therapy. For example, in the treatment of a case of delayed puberty in the male, the administration of androgen at an early age may assure fairly normal development insofar as secondary sexual characteristics are concerned but it will diminish the possibility of autonomous sustained control by the anterior pituitary of gonadal activity. Thus replacement therapy must be chronic, and there is little possibility of normal spermatogenesis. On the other hand, the longer one waits to treat a case of delayed puberty in the hope that spontaneous adolescence will occur, the less effective will be replacement therapy, if eventually it must be given.

The administration of androgens to immature male monkeys causes descent of the testicles. The ability of gonadotrophic hormones to cause descent of the testicles in immature monkeys and in certain cases of cryptorchidism in human beings may result secondarily from the release of androgen (page 1188).

If adequate amounts of androgen are injected into pregnant animals at certain critical stages, the female young exhibit intersexuality (Dantchakoff, 1936, *et. seq.*). This phenomenon occurs naturally in cattle and sheep in the case of the freemartin twin, and is due to the effect on the female of the secretory activity of the testis of the male twin in utero. Another outstanding action of the androgens is their ability to antagonize most of the actions of estrogens. For example, in women the administration of testosterone can suppress menstruation and cause hypoplasia or atrophy of the endometrium (Geist and coworkers, 1940). This has led to the therapeutic use of androgens in the treatment of such conditions as dysmenorrhea and menorrhagia, and for the suppression of lactation, etc.

Metabolic Effects. The androgens are chemically similar to the hormones of the adrenal cortex. Indeed, the secretions of the adrenal cortex and gonads share several actions in common. Thus hypersecretion of the adrenal cortex can cause virilism and sexual precociousness (page 1235). The androgens, in turn, exhibit some of the metabolic effects of the adrenal cortical hormones. For example, electrolyte metabolism is affected, the administration of testosterone causing a retention of extracellular electrolytes and fluid. The locus of action is probably the renal tubules. In addition, the excretion of nitrogen, inorganic phosphorus and potassium is diminished (Kenyon and coworkers, 1940), indicating a retention of essential cellular as well as extracellular constituents. The trophic action of androgens on the skeletal musculature is well known. Also of interest is the observation of Selye (1939, 1940) that the injection of testosterone in experimental animals causes marked enlargement of the kidneys and renders the organ less susceptible to toxic agents.

Absorption and Excretion. The absorption and excretion of testosterone propionate in man have been studied by Dorfman and Hamilton (1939). The substance gains ready access to the circulation from the gastro-intestinal tract as evidenced by the marked increase in the androgenic activity of the urine following the oral administration of testosterone. However, the therapeutic effects from this route of administration are poor, possibly due in part to the fact that the androgen is so rapidly absorbed and excreted. After the daily intramuscular injection of 20 mgm of testosterone propionate in peanut oil, the level of androgen excretion of a subject with deficient testicular function was raised to the normal of between 40 and 100 international units daily. The androgenic activity of the urine was approximately six per cent of the amount administered. This may indicate that a large portion of the injected material was destroyed in the body or that the testosterone was chemically changed and appeared in the urine in a less active form. The substance excreted in the urine is apparently in large part androsterone (Dorfman, Cook and Hamilton, 1939).

In clinical practice, testosterone has also been administered by inunction (Kearns, 1939) and by subcutaneous implantation of pellets (Vest and Howard, 1939).

Bio-assay and Unitage. There are a number of methods available for the bio-assay of androgens. The one most commonly employed depends upon the ability of the substance being tested to promote comb growth in capons. The international unit of androgen activity is that of 100 micrograms of crystalline androsterone. Inasmuch as the available preparations are crystalline in form, dosage is prescribed by weight rather than by units.

Preparations. Synthetic testosterone propionate is available for therapeutic use. This androgen is marketed by several firms under trade names (*see* Pratt, 1939). It is dispensed for parenteral administration in an oily solution containing five, 10 or 25 mgm per cc. Testicular extracts are also marketed but usually are not assayed. Their high cost and low potency do not recommend them for use.

Therapeutic Uses. The androgenic preparations have been used in therapeutics for so short a time that few definite conclusions can be drawn with respect to their value (*see* Council Report, 1939). There are certain conditions in which they may prove of definite benefit as already indicated by a limited experience. On the other hand, the older concepts concerning the male sex hormone, especially that of rejuvenation, are influencing modern therapy. Even now one can detect a definite trend toward emphasis on the ability of androgens to restore sexual activity. For example, they are recommended in advertising brochures for use in such vaguely defined conditions as the "male climacteric" and "atonicity." There is no doubt that the androgens, if improperly exploited, can do much harm.

A few isolated but encouraging reports have appeared on the use of male sex hormone in the replacement therapy of *prepuberal and postpuberal castrates* (*see* McCullagh, 1939; Howard and Vest, 1939; Eidelsberg and Ornstein, 1940). If androgen is given to the postpuberal castrate, it is possible to restore masculinity and overcome many, if not all, of the signs and symptoms of the syndrome. If androgen is given long after the normal time of maturity to the prepuberal castrate, it is not possible to overcome all the manifestations of the deficiency, but definite improvement can be noted. Accompanying the physical changes, there is a marked change for the better in the mental outlook of the castrate as evidenced in some patients. Dosage is adjusted to the individual case. An average dose which may have to be altered is 20 mgm of testosterone propionate in oil injected intramuscularly daily. At present, the cost is often prohibitive in many cases because therapy is purely replacement in character and must be continued to maintain results. It may be possible to implant pellets of crystalline testosterone under the skin of patients and maintain therapeutic benefit for many weeks. Should this technic prove feasible, it would reduce the cost of therapy and eliminate the necessity of daily injections of the drug.

There is some clinical evidence that androgens may prove of limited value in the treatment of *cryptorchidism.* It may be that the beneficial effect of the gonadotrophic substances rests upon their ability to stimulate production of androgen. If therapy with testosterone is attempted, the dose level may be started at 10 mgm in oil administered parenterally three times weekly. The patient should be observed closely and treatment should not be prolonged more than six weeks.

On rather incomplete evidence, testosterone has been recommended for the treatment of *prostatic hypertrophy.* However, there is little evidence that the administration of androgens can cause involution of an existing hypertrophy (*see* Heckel, 1940; Creevy and Rea, 1940) and there is always the possibility that the male sex hormone in itself may cause a still greater enlargement of the gland. There is some indication that nocturia, dribbling and control of the urinary stream may be benefited by androgen medication, but the effect may well be secondary to a generalized improvement in muscle tone and other changes rather than the result of any action solely on the prostate (Hamilton and Gilbert, 1938).

Androgenic therapy has not been limited to males. Testosterone propionate has been employed for the treatment of *dysmenorrhea.* If the dose is large or too long continued, a significant degree of virilism may develop which is slow in regressing and the voice may not return to normal (Greenhill and Freed, 1939; Geist and coworkers, 1940). Androgens have also been employed for relief of *menopausal states, peripheral vascular disease, painful breasts, menorrhagias, and to produce interruption of lactation.* More clinical evidence is necessary before the hormone can be considered safe and of value in these conditions and before the mechanism of action can be stated.

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CHAPTER 68

INSULIN

History. Although many of the clinical features of diabetes mellitus had been known for centuries, it was the classic experiment of von Mering and Minkowski (1890) that established the relationship of the pancreas to this disease. These investigators observed many of the features of clinical diabetes following pancreatectomy in experimental animals. Even after this convincing demonstration, there were some who believed that the trauma of the operation, especially to nerves, might account for the results obtained. Hedon (1894) removed this doubt by demonstrating that the subcutaneous transplantation of part of the pancreas, devoid of nervous connections, could prevent the onset of the symptoms of diabetes. This observation left no doubt as to the importance of the pancreas in the metabolism of carbohydrate, but it still allowed for two interpretations as to the possible function of the organ. It was commonly believed that the pancreas secreted a substance which was necessary for the combustion of carbohydrate, but some were of the opinion that pancreatic function was one of detoxification to remove a factor which interfered with normal carbohydrate metabolism.

In order to prove the first theory, attempts were made to obtain from the pancreas an extract containing a substance which could support life in the absence of the organ. Confident of its existence, de Meyer (1909) named this hypothetical substance "Insuline." Attempts to isolate "Insuline" met with repeated failure and this was interpreted either as favoring the second theory, or as an indication that "Insuline" was not stored in sufficient quantity to allow for its extraction.

In the light of present knowledge, the reason for these failures is known. Insulin, the active principle of the pancreas, is a protein, and its activity depends upon the integrity of the protein structure. The pancreas is also the site of formation of the proteolytic enzyme trypsin. It is now apparent that in the early attempts at isolation insulin was being digested as rapidly as it was extracted. This fact was suspected by Banting who reasoned that if the pancreatic ducts were ligated and the acinous tissue of the gland allowed to degenerate the principle acting on carbohydrate metabolism might be obtained in an active form. Banting and Best (1922) attempted this experiment and their success is now medical history. They also succeeded in obtaining active extracts from fetal pancreas in which the cells secreting enzyme had not yet developed.

It is no longer necessary to obtain insulin from degenerated or fetal glands. The knowledge that insulin is destroyed by enzymatic digestion pointed the way for chemists to extract the pancreas in such a manner as to avoid the proteolytic action.

Chemistry. Insulin is a protein with a molecular weight of 41,000. The amino acids leucine, glutamic acid, cystine, tyrosine, histidine, arginine, lysine, proline, phenylalanine and possibly methionine have been established as constituents of the molecule. A great deal of interest has centered on the relationship of the structure of insulin to its action. In the case of the hormone thyroglobulin, much of the activity can be attributed to the amino acid thyroxin. No particular type of chemical configuration or special amino acid, however, has been found to account for insulin activity. Furthermore, little can be done chemically to the molecule before all pharmacodynamic action is lost.

For example, hydrolysis with acid or enzymes results in a complete loss of activity. For this reason insulin is ineffective if given by mouth. If the phenolic hydroxy groupings contained in the tyrosine of insulin are acetylated, there is a reduction of physiological activity proportional to the number of blocked hydroxy groups (Stern and White, 1937). Reduction of the insulin molecule also leads to a loss in activity. One molecule of insulin contains 18 oxidized sulfur linkages (S-S). If only one or two of these are reduced to the SH form, the physiological activity is halved. Early investigation pointed to the necessity of free amino groups for the activity of insulin. Later reports (Stern and White, 1937) showed that if the amino groups are acetylated, it is possible to mask completely all the free amino groups without loss of insulin activity. A detailed discussion of the chemistry of insulin may be found in the monograph of Jensen (1938).

All investigations point to the marked specificity of chemical structure necessary for insulin action. The possibility of obtaining an active insulin fraction of simple composition appears to be remote. Seemingly the configuration of the protein molecule as a whole is necessary for physiological activity.

Hypoinsulinism. The concentration of insulin in the body is delicately adjusted by an internal mechanism yet to be elucidated. It is thought that the concentration of sugar in the blood flowing through the pancreas is the factor which regulates the rate at which insulin is discharged into the blood stream. This concept receives support from the observation that the pancreas, even when it is transplanted to a foreign site and is devoid of nervous connections, is capable of maintaining an optimal concentration of insulin.

When the pancreas is extirpated, or the cells of the islet tissue which form insulin lose their function, the concentration of insulin in the body fluids falls, and hypoinsulinemia results. The condition of hypoinsulinemia leads to the well-known symptoms of diabetes mellitus, such as polyuria, polydipsia, polyphagia, loss of weight and weakness. The concentration of sugar in the blood rises rapidly, the renal threshold for glucose is exceeded and a glycosuria results. The respiratory quotient falls. A disturbance in fat metabolism is manifest in a variety of ways. There is an increase in the ketone bodies in the blood and these are excreted into the urine. The particular intermediary products of fat metabolism which accumulate are acetone, beta-oxybutyric acid and acetoacetic acid. The two latter substances contribute to the acidosis often characterizing severe diabetes. In addition, aceto-acetic acid is a powerful respiratory stimulant and may contribute to the dyspnea of diabetic acidosis. The mobilization of fat is increased in diabetes. The fat depots of the body are diminished and the concentration of neutral fat, phospholipids and cholesterol esters in the blood rises. A large amount of fluid is necessary to excrete the glucose which appears in the urine and diuresis results. The urine also contains appreciable amounts of organic acids and sodium and this leads to a depletion of extracellular base. The organic acids in the blood stream displace bicarbonate and even chloride. As a result the blood chemistry is distorted and severe diabetic coma is characterized by acidosis, low serum electrolyte concentration and anhydremia. Vomiting is also common and this adds to the disturbance in blood chemistry.

Hyperinsulinism. Hyperinsulinism commonly results from improper medication with insulin. Occasionally, however, an adenoma of the pancreas may be the cause and requires surgical removal. The blood sugar falls and the symptoms are the result of the hypoglycemia. These have been outlined by Geiling, Jensen, and Farrar (1937) as follows:

1. NERVOUS
   (a) Autonomic: Sweating, pallor, flushing, salivation, tachycardia.
   (b) Psychic: Anxiety, confusion, irritability, negativism, dullness, excitement, violence.
   (c) Bulbo-pontine: Stammering and other speech disorders, diplopia, nystagmus, anisocoria.

(d) Cortico-spinal: Tremor, transient paralysis, positive Babinski sign, aphasia, incoordination, twitching, convulsions, epilepsy-like condition.

2. GASTRO-INTESTINAL
   Epigastric sinking sensations, hunger, increase in hunger contractions at blood levels down to 75 mgm per cent, gastric atony below that level, occasionally vomiting.
3. CARDIOVASCULAR
   Tachycardia and extrasystoles, slight rise in blood pressure, anginal attacks in patients with damaged myocardium.

The majority of the symptoms originate in the central nervous system and the actions of insulin at this site have been extensively investigated. During hypoglycemia the oxygen consumption of the brain is markedly diminished. The respiratory quotient of the brain is unity and seemingly this tissue can metabolize only carbohydrates. Himwich and Fazekas (1937) believe, therefore, that the diminution in oxygen consumption is due to the lack of substrate. Sherrill and MacKay (1937) observed that animals in insulin shock over long periods of time cannot be revived, due to extensive damage to the central nervous system. Yannet (1939) studied in greater detail the effects of prolonged hypoglycemia produced by insulin. He observed that if the blood sugar is depressed by large doses of insulin and animals remain in "insulin shock" for 12 hours or longer, irreversible damage can occur to the brain as evidenced by the destruction of ganglion cells of the cortex, basal ganglia and rostral parts of the medulla. Animals surviving long periods of hypoglycemia present, after recovery, the typical symptoms of functional decortication. The essential features of these experiments have been adequately confirmed by other investigators (Baker, 1939; Ziskind and Tyler, 1940).

Yannet (1939) also observed in cats a marked hydration of the cells of the brain coincidental with the symptoms of "insulin shock." Another interesting observation was that the blood pressure was maintained at a normal level until just before death, a corroboration of clinical findings. Therefore the term "insulin shock" should not be regarded as referring to the condition of the circulation.

Although the symptoms of insulin hypoglycemia seem well defined, it is often difficult clinically to distinguish this condition from diabetic coma. Many cases of insulin shock have been treated with insulin. The differential diagnostic points between diabetic acidosis and insulin reactions are presented in Table 60. The symptoms of hypoglycemia yield almost immediately to the intravenous injection of dextrose.

Mechanism of Insulin Action. Despite the vast amount of research on this subject, it is impossible to state didactically the basic mechanism of insulin action. There is convincing evidence that insulin in some manner promotes the oxidation of carbohydrate and is an essential in the intermediary metabolism of this important source of energy. In a depancreatized animal, insulin increases oxygen utilization, raises the respiratory quotient and lowers the blood sugar. Krebs and Eggleston (1938) have demonstrated the ability of insulin to promote the oxidation of glucose *in vitro*. The particular phase of carbohydrate metabolism which is influenced by insulin is not known, however, and this is not surprising inasmuch as there is no unanimity of opinion in regard to the course of the intermediary metabolism of sugars.

There is also evidence that insulin regulates the formation of sugar from non-carbohydrate sources. In addition to the data obtained from the innumerable studies on diabetic human beings and depancreatized animals, *in vitro* experiments of Bach and Holmes (1937) demonstrate that, in the absence of insulin,

TABLE 60

DIFFERENTIAL DIAGNOSIS OF DIABETIC ACIDOSIS AND INSULIN REACTIONS

	DIABETIC ACIDOSIS	INSULIN REACTIONS	
		REGULAR INSULIN	PROTAMINE ZINC INSULIN
Onset	Slow, 12 hrs. to two or more days	Sudden, minutes	Gradual, minutes to hours
Premonitory symptoms and mental state	Anorexia, nausea, headache, restless, distressed, gradually approaching unconsciousness	Hunger which is often extreme; irritable, hysterical, gradually approaching unconsciousness	Headache, aphasia, emotional instability, gradually approaching unconsciousness
Appearance	Florid, extremely ill	Pale, weak, faint	Pale, weak, faint
Food	Too much	Too little	Too little
Insulin	Too little	Too much	Too much
Presence of infection	Usual	None	None
Thirst	Extreme	Absent	Absent
Vomiting	Common	Absent	Infrequent
Pain in abdomen	Frequent	Absent	Rare
Skin	Dry	Moist	Normal or moist
Tremor	Absent	Frequent	Frequent
Convulsions	Rare	Occasionally (late)	Occasionally; may be first symptom
Vision	Dim	Disturbed; often double	Disturbed
Eyes	"Soft eyeballs"	Normal	Normal
Pupils	Dilated	Normal or dilated	Normal or dilated
Respiration	Deep, sighing (air hunger)	Normal	Normal
Breath	Odor of acetone	Normal	Normal
Blood pressure	Subnormal	Normal or elevated	Elevated
Temperature	Subnormal, rapid rise	Subnormal	Subnormal
Urine	Sugar, acetone, aceto-acetic acid	Sugar absent, or always absent in second of two specimens	No sugar, acetone or aceto-acetic acid
Blood chemistry	Hyperglycemia; low CO_2 combining power	Hypoglycemia; normal CO_2 combining power	Hypoglycemia; normal CO_2 combining power
White blood cells	Increased	Normal	Normal
Response to treatment	No response to glucose; gradual improvement in hours with insulin	Sudden improvement in minutes with carbohydrate by mouth, or or glucose by rectum, intravenously or subcutaneously	Prompt improvement in minutes after glucose therapy; may have relapse

liver slices taken from starved rats form sugar from antiketogenic amino acids much more rapidly than when the hormone is present. Thus it appears probable that insulin has a dual mechanism of action in the body, and the hormone both promotes the oxidation and decreases the production of carbohydrate.

Effects of Other Endocrine Organs. No discussion of the mechanism of insulin action would be complete without mentioning the effects which other endocrines exert on carbohydrate metabolism and their possible relationship both to insulin action and the etiology of diabetes. Largely through the investigations stimulated by the initial reports of Evans and collaborators (1932) and of Houssay and associates (1932) it has been ascertained that the hormones of the anterior pituitary are closely linked with carbohydrate metabolism. The administration of large amounts of *anterior pituitary* extract produces glycosuria and hyperglycemia and renders certain species of animals relatively insensitive to insulin. Conversely, the hypophysectomized animal has a characteristically low blood sugar, suffers from hypoglycemic convulsions if deprived of food and is abnormally sensitive to insulin. Lastly, the symptoms of diabetes in depancreatized animals are greatly ameliorated by hypophysectomy, and the hypophysectomized-depancreatized animal survives much longer without endocrine therapy than does the depancreatized control.

The *adrenal cortex* also has a marked effect on carbohydrate metabolism. Britton (1938) long contended that the primary function of the adrenal cortex is in the regulation of carbohydrate metabolism. He demonstrated that in the absence of the adrenal cortex there follows a hypoglycemia and a reduction in liver and muscle glycogen. Adrenalectomized animals lose their ability to deposit glycogen but this can be restored by the administration of a potent extract of the gland.

The fact that, in the absence of the anterior pituitary, atrophy of the adrenal cortex occurs led Long and Lukens (1936) to a study of the relationship between the adrenal cortex and pancreas with respect to carbohydrate metabolism. They found that the adrenalectomized-depancreatized animal maintained on sufficient cortical extract to support life was similar in many respects to the hypophysectomized-depancreatized subject. The adrenalectomized-depancreatized animal when compared with the depancreatized animal excretes less glucose, nitrogen, and acetone bodies and fails to develop acidosis. Long, Fry and Thompson (1938) showed that the symptoms of diabetes exhibited by partially depancreatized rats can be alleviated by the removal of the adrenal glands and the diabetic state can be restored either by the administration of cortical extracts or by implantation of cortical tissue.

The mechanisms by which the anterior pituitary and adrenal cortex influence carbohydrate metabolism cannot be stated with certainty. Whether the anterior pituitary exerts its entire effect through a stimulation of the adrenal cortex or is directly concerned in the metabolism of carbohydrate is also a subject of dispute. Seemingly, the anterior pituitary and the adrenal cortex, on the one hand, and the pancreas, on the other, have antagonistic actions with respect to their influences on carbohydrate metabolism. Whether their point of action is on the actual combustion of carbohydrate or on the conversion processes of other foodstuffs to sugar (page 1236) cannot be stated definitely. The interested reader is referred to the reviews of Long (1937, 1939) and Russell (1938) for a detailed discussion of this field of research.

Other endocrine glands also affect carbohydrate metabolism, although probably not to the degree of the anterior pituitary and the adrenal cortex. Thus epinephrine increases the breakdown of glycogen and redistributes formed carbohydrate. Thyroxin increases the rate of oxidation of glucose in tissues and the rate of glycogen formation in the liver. The endocrine control of carbohydrate metabolism is schematically represented in Figure 112.

The interrelationships of the endocrines in the control of carbohydrate metabolism are still primarily an academic subject. The newer knowledge has not changed the therapy of the diabetic syndrome. It has, however, broadened the concept of the pathological physiology of diabetes. The fact is now appreciated that the disease need not be of pancreatic origin. Hyperfunction of the pituitary or adrenals can as feasibly produce abnormalities of carbohydrate metabolism as can hypofunction of the pancreas. Abnormal pituitary function is probably the reason for the high incidence of glycosuria in individuals suffering from acromegaly (*see* review of Coggeshall and Root, 1940), and may be related to the relatively high incidence of juvenile diabetes mellitus at puberty, and following periods of excessive growth. It may also account for the large number of cases of diabetes occurring in women at the time of the menopause. In the past, the fact that no relationship has been found to exist between the degree of pathological change in the islet tissue of the pancreas and the severity of the diabetic syndrome has been difficult to interpret. This discrepancy perhaps can be explained if one accepts the clinical significance of the experimental results on animals concerning the rôle of hormones other than insulin in the regulation of carbohydrate metabolism. Also the newer knowledge reëmphasizes the necessity for individual therapy in the treatment of diabetes and each case requires study with respect to its management. Two individuals showing an equally severe abnormality in carbohydrate metabolism may vary widely in their insulin requirements because the origin of their symptoms may be in the abnormal function of different glands.

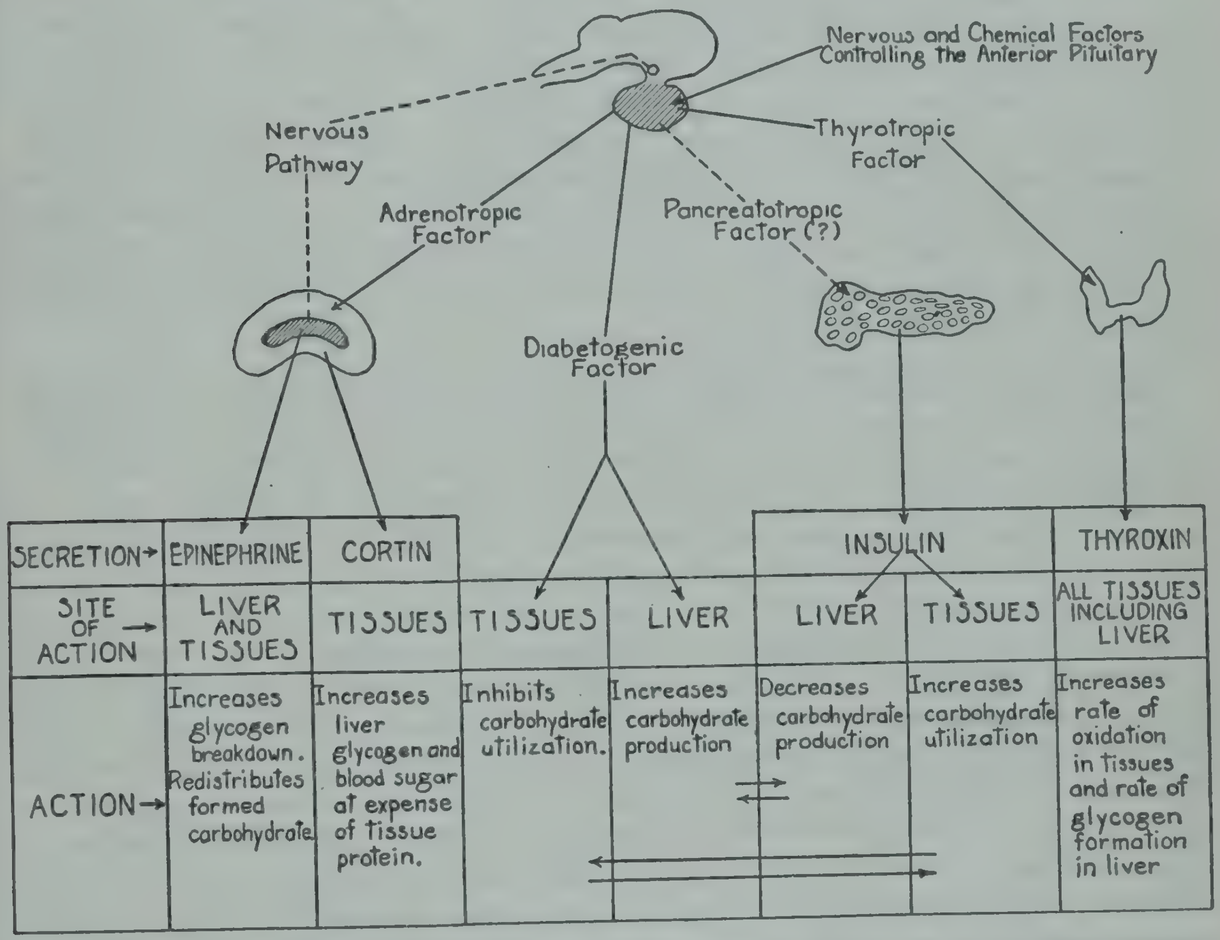
Nervous and Chemical Factors Controlling the Anterior Pituitary
Nervous Pathway
Thyrotropic Factor
Adrenotropic Factor
Pancreatotropic Factor (?)
Diabetogenic Factor
SECRETION→
EPINEPHRINE
CORTIN
INSULIN
THYROXIN
SITE OF ACTION →
LIVER AND TISSUES
TISSUES
TISSUES
LIVER
LIVER
TISSUES
ALL TISSUES INCLUDING LIVER
ACTION→
Increases glycogen breakdown. Redistributes formed carbohydrate
Increases liver glycogen and blood sugar at expense of tissue protein.
Inhibits carbohydrate utilization.
Increases carbohydrate production
Decreases carbohydrate production
Increases carbohydrate utilization
Increases rate of oxidation in tissues and rate of glycogen formation in liver

FIGURE 112. *Schematic diagram illustrating the endocrine control of carbohydrate metabolism.* (After Long, 1938. Courtesy of the *Sigma Xi Quarterly*.)

Absorption, Fate and Excretion. In order to be effective, insulin must be given parenterally. After the oral administration of huge doses, some of the compound may escape destruction and reach the circulation. The uncertainties attending this route of administration, however, are so great as to render it clinically valueless. Likewise, absorption from other mucous membranes is too capricious to permit therapeutic administration by these routes. After subcutaneous, intramuscular or intraperitoneal injection, insulin in an active form rapidly gains access to the circulation. The subcutaneous route is employed clinically. The onset of action is almost immediate and the maximal effect is obtained after one to three hours (Figure 113). Insulin is rapidly destroyed in the body. A small amount may be excreted in the urine. Injected insulin probably disappears completely from the body within eight hours. After intravenous injection, the rate of excretion and destruction is more rapid.

Factors Regulating the Rate of Insulin Absorption. As chemical methods for the isolation and purification of insulin have improved, the duration of action of the resulting preparations has decreased. This is probably due to the increased rate of absorption of the more purified products. The early crude insulin preparations were likely to produce local reactions, but at the same time they exerted their beneficial effects over many hours.

In the normal individual, insulin is continuously liberated by the pancreas in small amounts. The concentration of hormone in the blood of the diabetic who must rely on an external source of insulin shows great variations, being high subsequent to and low immediately prior to an injection. As a consequence, the level of blood sugar may vary widely from the normal. At times it may be so high as to exceed the renal threshold and at other times fall so low as to necessitate the ingestion of carbohydrate in order to avoid the symptoms of hypoglycemia. It has long been recognized that retardation in the rate of absorption of insulin would do much to overcome this undesirable feature and allow a more constant blood insulin level. In the past various measures have been employed to influence the rate of absorption. Thus, insulin has been injected in gum arabic solutions, in lecithin emulsions, in oily suspensions, in conjunction with epinephrine and posterior pituitary extract, and with astringent metals. None of these procedures has proved practical.

Protamine Insulin. A practical method for retarding the rate of insulin absorption was introduced by Hagedorn and his coworkers (1936). The isoelectric point of insulin is at pH 5.35. In general, it may be stated that the solubility of a protein is minimal at a reaction approximating the isoelectric point and increases as the solution becomes more acid or alkaline. Thus at the pH of the body insulin is readily soluble and rapidly absorbed.

Proteins combine with the basic protein structures known as *protamines* to form salts. The salt of insulin and protamine is known as *protamine insulin.* The isoelectric point of this compound is at pH 7.3 and therefore it is relatively insoluble at the pH of the body fluids. When solutions of protamine and insulin are mixed in a buffered solution at the isoelectric point, a flocculent precipitate is formed. If this is administered subcutaneously in the form of a suspension, solution is slowly effected at the site of injection, and the insulin is absorbed at a retarded but steady rate (Figure 113). The rate at which the hormone gains access to the circulation probably more closely approximates the normal rate of physiological discharge from the pancreas. Therefore, the duration of action is longer and fewer injections are required, the concentration of sugar in the blood stays more closely within normal limits, glycosuria and ketonuria are more efficiently controlled, and the incidence of hypoglycemic reactions is reduced.

Protamine Zinc Insulin. The suspension of protamine insulin is not stable for long periods. After a few days, the material tends to adhere to the vial and it is impossible to obtain a homogeneous suspension. Scott and Fisher (1936) observed that the addition of a small amount of zinc serves to stabilize protamine insulin. *Protamine zinc insulin* can be used for six months after preparation, whereas in the absence of zinc the protamine salt must be freshly prepared. Also, protamine zinc insulin is absorbed less rapidly than protamine insulin. Protamine zinc insulin has therefore largely replaced protamine insulin in therapeutics. The rôle of zinc in the crystallization of insulin is discussed under zinc.

Bio-assay and Unitage. Insulin preparations must be subjected to bio-assay in order to ascertain their physiological activity. The rabbit is used as the test animal. The activity of samples is determined by their ability to lower the blood sugar. The details of the assay are given in New and Nonofficial Remedies. The potency is expressed in units and the standard of comparison is crystalline insulin, the activity of which is 22 international units per milligram.

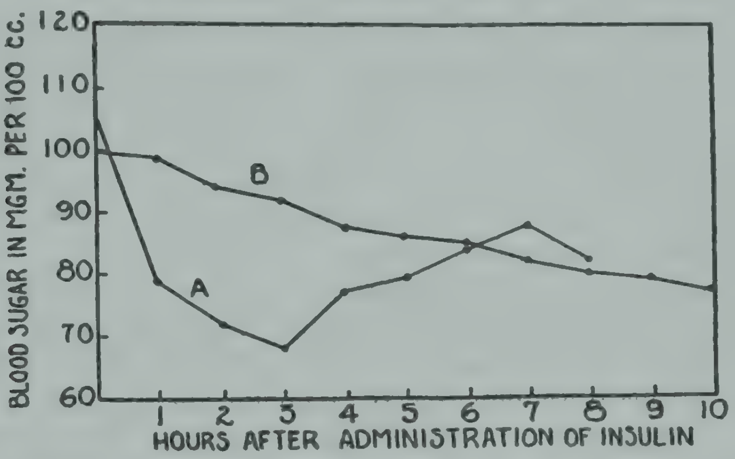

FIGURE 113. *The comparative effects of the subcutaneous injection of regular insulin and protamine insulin on the blood sugar of a normal woman.*

A. Eight units of regular insulin. *B.* Same amount of protamine insulin. The insulins were injected at zero time, and on two different days. Note the gradual and steady fall in blood sugar after protamine insulin. The blood sugar had not yet reached its lowest level at the time when the effects of regular insulin had subsided. (After Root, White and Marble, 1936. Courtesy of *The Journal of the American Medical Association.*)

Preparations. Insulin does not appear in the U.S.P. because its manufacture is still covered by patents. There are many preparations, however, which are included in N.N.R. and the drug is official in the B.P. Inasmuch as insulin must be given by subcutaneous administration it is desirable to limit the volume of fluid injected to less than one cc. Because the insulin requirements of diabetics vary widely, preparations are available in strengths of 10, 20, 40, 80, and 100 units per cc. *Protamine Zinc Insulin,* N.N.R., can be obtained in the concentrations of 40 and 80 units per cc. Sterile hypodermic tablets of insulin are official in the B.P.

Insulin is usually isolated from the pancreas as an amorphous powder. The hormone can be readily crystallized, however, in the presence of zinc. *Solutions of crystalline zinc insulin* are marketed commercially and should not be confused with preparations of protamine zinc insulin. The actions of crystalline zinc insulin are only slightly different from those of amorphous insulin and the compound possesses no therapeutic advantages over amorphous ("regular") insulin (Ricketts and Wilder, 1939; Marble and Vartiainen, 1939).

Therapeutic Uses. Diabetes Mellitus. The treatment of diabetes mellitus depends so much on the individual problem presented by the particular patient that it is almost impossible to state fixed rules of therapy. One patient may require only a single injection of a few units of insulin a day and another may need two or three large doses. In one individual, a unit of insulin will promote the oxidation of more carbohydrate than in another. However, in all cases the therapeutic objective is the same, namely, to allow the patient to live a normal life and remain symptom-free.

Many patients with mild diabetes mellitus can be treated by diet alone. The diet, as a rule, is constructed to contain sufficient calories, at least 0.75 to 1.0 gram of protein per kg of body weight (for adults), and approximately 100 grams of carbohydrate. If sugar is still present in the urine, it is usually considered best to use insulin rather than to restrict carbohydrate to a point where the diet is unpalatable and induces constant ketosis.

An approximation of the amount of insulin necessary in a given case may be ascertained from the amount of glucose which is excreted in the urine. It may be roughly estimated that one unit of insulin is required for every 1.5 to 2.0 grams of glucose in the urine in order to render an individual aglycosuric. It must be emphasized that this is only an approximation and actually the amount of insulin necessary may vary greatly on either side of the figure quoted. Therefore, unless the patient can be under constant observation during the period that his insulin dose is being adjusted, only one-half the calculated amount of hormone should be given. The dose may be increased only after more information is obtained concerning the patient's insulin tolerance.

If the insulin requirements of a patient are low, a single dose daily usually suffices. This should be given before breakfast, the time when the blood sugar is usually at its highest level. If moderate amounts (less than 40 units daily) are required, injections are most effective if given before the morning and evening meals. Individuals requiring 40 units or more daily usually must receive insulin before each meal. At times it is necessary to give a few units before retiring.

Factors Influencing Insulin Action and Modifying Dosage. The factors which modify carbohydrate metabolism and influence the action of insulin must be taken into account in the therapeutic use of the hormone.

The *route of administration* determines the rapidity and duration of insulin action. Patients are taught to give themselves injections aseptically by the subcutaneous route, but in diabetic coma intravenous injection is often employed by the physician to insure adequate absorption and rapid action. The patient is warned not to give himself injections repeatedly at the same site for this may result in local reactions which retard absorption. The diabetic should be urged to keep an injection map in order to avoid this occurrence. A convenient site of administration is under the skin of the thighs.

Muscular activity leads to a greater utilization of carbohydrate. Thus, a patient doing well on a given dose of insulin is likely to suffer from a hypoglycemic episode if he overexercises. It is therefore necessary to regulate the activities as well as the diet of a diabetic patient receiving insulin. Exercise need not be restricted but rather the insulin dosage and carbohydrate intake must be adjusted to the total metabolic requirements. It is important to remember the effect of muscular activity because the insulin requirement of a patient is often determined during hospitalization under sedentary conditions.

Infection also influences the action of insulin, definitely reducing the sensitivity of an individual to the hormone. The mechanism involved is unknown but it is believed that circulating toxins in some way interfere with insulin activity. In the presence of infection, the insulin dosage must be increased. It is especially important to control the blood sugar under such conditions for it appears that hyperglycemia may favor the spread of certain infectious processes.

Acidosis also decreases insulin activity. If the pH of the blood falls, more insulin is necessary to metabolize a given amount of sugar. Thus, in the treatment of diabetic acidosis, unusually high amounts of insulin are required.

Fever, especially when not of infectious origin, decreases the insulin requirements in a manner probably similar to exercise. The increase in metabolic rate accompanying hyperthermia seemingly favors oxidation of carbohydrate.

Anesthesia increases the need for insulin and this fact is to be considered before operating upon a diabetic. The decreased sensitivity to insulin is probably the combined result of acidosis and epinephrine discharge during anesthesia. The preoperative and postoperative care of the patient with diabetes has been reviewed by McKittrick and Root (1940).

The *glucose tolerance* is probably the most important factor determining the insulin requirement, and the diet prior to the test for this tolerance often influences the result obtained. The glucose tolerance largely determines the initial dosage of insulin. Obviously, a mild diabetic with a tolerance for glucose only slightly lower than normal requires little or no hormone. It is important to remember, however, that the glucose tolerance may change markedly and there is no assurance that a given dose of insulin will remain optimal. After a period of insulin treatment, some individuals may improve and need only dietary therapy. The insulin requirements of others may grow progressively larger.

Menstruation tends to increase the need for insulin and the dosage occasionally may have to be increased during this period. *Emotional stress* or *nervous tension* often affects carbohydrate metabolism and individuals of uneven temperament are likely to present difficult therapeutic problems.

Allergic reactions to insulin are sometimes troublesome in therapy. These commonly take the form of severe local reactions at the site of injection. They usually disappear gradually within the course of a few weeks. If they persist, it may be necessary to use the insulin marketed by a different firm, or if this fails the hormone prepared from the pancreas of a different species of animal may be required. An occasional patient may become sensitized to insulin after a change is made from regular to protamine insulin, possibly as a result of the slower absorption of the antigen (Kern and Langner, 1939).

Diabetic Diet. The diet of a diabetic individual is the main factor which determines the dose of insulin. The diet must contain an adequate amount of total calories, protein, minerals and vitamins. However, it can vary widely with respect to the proportion of calories received from fat and carbohydrate. Before the discovery of insulin, invariably the diabetic diet was high in fat and low in carbohydrate. This reduced the excretion of glucose but greatly favored the development of acidosis. The carbohydrate ration is now more liberal because it is possible to metabolize this foodstuff with the aid of extraneous hormone. In the case of the mild diabetic who has a fair carbohydrate tolerance and can avoid the necessity of insulin by proper dietary management, it is justifiable to lower the carbohydrate and raise the fat intake so that the urine remains glucose-free. Limits to dietary therapy are set by the distastefulness of diets low in carbohydrate, and the degree of ketosis which results. In the more severe cases, however, a more liberal carbohydrate intake is allowed and sufficient insulin is given to assure proper combustion. As the content of carbohydrate in the diet is increased, the amount of insulin required for its metabolism is not proportionately raised. Therefore, many advocate a high carbohydrate diet for diabetics inasmuch as little more insulin is necessary than if the diet were more rigidly restricted. For a complete discussion of this subject the reader is referred to texts dealing in detail with the management of diabetes (*see* Joslin, 1937).

Protamine Zinc Insulin in the Treatment of Diabetes. It is often difficult to maintain an even blood sugar level with ordinary insulin due to the fact that it is rapidly absorbed and destroyed. In severe cases of diabetes, therefore, insulin must be administered several times a day. During the night, the blood sugar rises and morning glycosuria is common. Protamine zinc insulin is a preparation which in the hands of the skillful practitioner can overcome these disadvantages. Due to its slow and even rate of absorption, protamine zinc insulin exerts it effects for 24 hours. The objective in using the preparation is to reduce, if possible, the number of injections to one daily and maintain a more even blood sugar con-

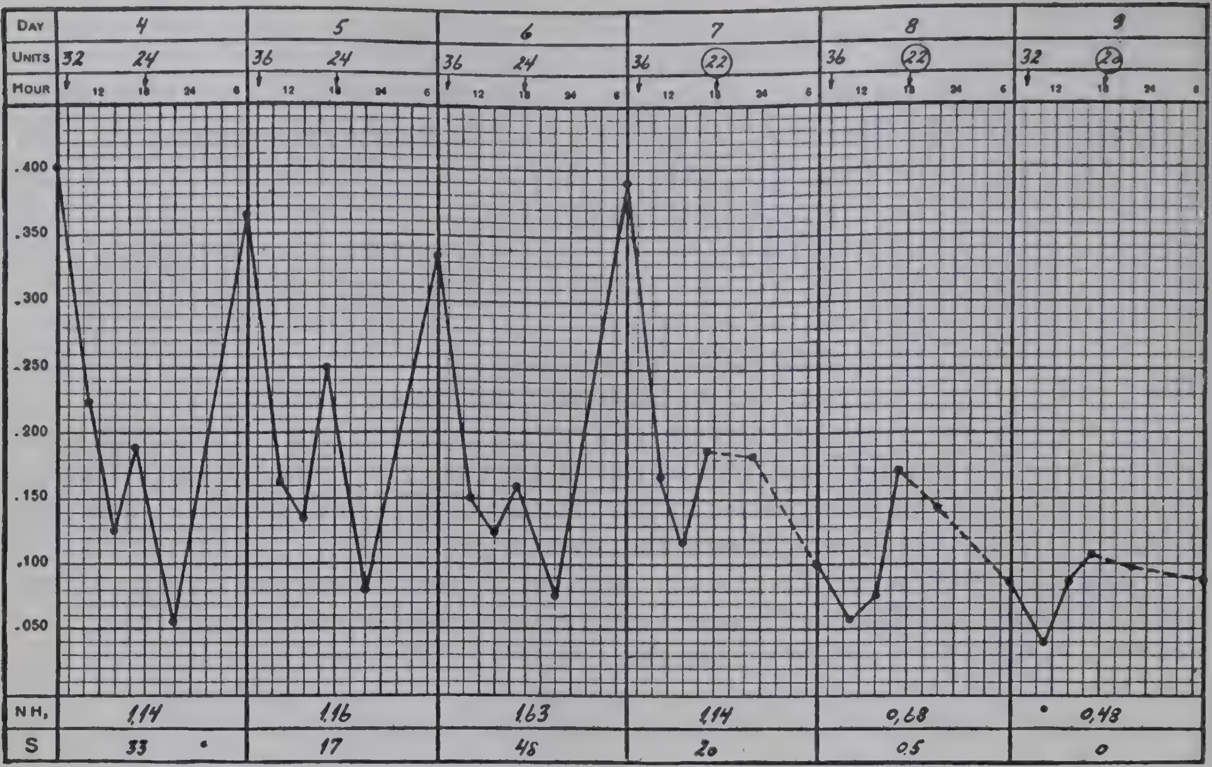

Figure 114. *The clinical effects of ordinary insulin compared with those of protamine insulin in a patient with diabetes mellitus, from the original report by Hagedorn and associates.*

The dose of insulin in units is indicated below the days of treatment. A circle around the figure signifies that protamine insulin was employed. The arrow appearing below the dose of insulin marks the time of injection. The blood sugar is given in per cent along the axis of ordinates. The excretion of ammonia and of sugar in grams per 24 hours is indicated at the bottom of the figure. A broken line signifies that protamine insulin was given. Note the wide fluctuations in blood sugar and the high excretion of ammonia and sugar during the first three days when ordinary insulin alone was administered. Compare these events with the smoother control of blood sugar levels and the lessened excretion of ammonia and sugar when protamine insulin was given in conjunction with ordinary insulin. The diet contained 70 grams of protein and 100 grams of carbohydrate, 20 per cent of the latter being given at the evening meal and the remainder in equal portions at breakfast and lunch. (After Hagedorn, Jensen, Krarup and Wodstrup, 1936. Courtesy of *The Journal of the American Medical Association.*)

centration. The amount required is usually slightly less than when ordinary insulin is used (Figure 114).

The rate of absorption and duration of action of protamine zinc insulin necessitate certain dietary adjustments. The carbohydrate content of the meal immediately following the injection is usually kept low because a considerable period of time is required before maximal effects are obtained. It requires co-operation and intelligence on the part of the patient to adjust himself to the preparation, especially if he has become accustomed to ordinary insulin; but the results justify the effort. Figure 114 compares the effects of ordinary and protamine insulin on the concentration of blood sugar of a diabetic patient over 24-hour periods.

Hypoglycemic reactions are significantly fewer with the use of protamine zinc insulin. When they do occur, however, they are likely to be prolonged due to the fact that continuous absorption of hormone is taking place. Unusual exercise is likely to cause a severe hypoglycemic reaction in patients receiving this form of insulin. The best treatment is prophylactic and the patient should anticipate increased metabolic activity by taking an excess of carbohydrate. When ordinary insulin is used, the dosage can be reduced in anticipation of exercise.

Diabetic Coma. Insulin is specific in the treatment of diabetic coma. The administration of the hormone, however, is only part of the therapy because the patient may be in shock. The distortion in the chemistry and distribution of body fluids is the immediate cause of symptoms and efforts should be directed to restoring a normal internal environment (*see* page 591 for further details). This can best be accomplished by the administration of large amounts of isotonic saline. Unless the acidosis is extremely severe (Figure 115), it is not necessary to administer alkalis, for it should be recalled that much of the base of the extracellular fluids is combined with organic acids. Once the ability to oxidize these acids is reëstablished by the administration of insulin, large amounts of alkali will become available. Therefore, the injection of sodium bicarbonate or sodium lactate is likely to result in alkalosis.

Insulin is usually administered both intravenously and subcutaneously. The amount necessary is largely determined by the individual response, as measured clinically by repeated estimations of blood sugar, carbon dioxide combining power of the plasma, and urinary sugar and acetoacetic acid. An average initial dose may be between 20 and 40 units. Intravenous administration is usually limited to those cases in which an impaired circulation is likely to retard absorption. Many clinicians now use protamine zinc insulin in conjunction with ordinary insulin in the treatment of diabetic coma. After the effects of the regular insulin have disappeared, the slow even absorption of protamine zinc insulin can control the later stages of therapy. Kepler (1938) advises that in the treatment of diabetic coma a large dose of protamine zinc insulin be administered immediately and then regular insulin used as though no insulin had been given. Once the coma is under control, the patient seldom escapes from insulin action due to the continuous absorption of protamine zinc insulin (Figure 115).

There is a difference of opinion as to whether glucose should be given with insulin in the treatment of diabetic coma. It probably simplifies therapy to administer one gram of glucose for every unit of insulin injected. If the glucose is given in hypertonic solution it helps to restore the volume of the circulation which may be low due to the electrolyte disturbance.

Miscellaneous Uses of Insulin. Insulin has been used in the treatment of a number of nondiabetic conditions. The hormone has been rather extensively employed in cases of *impaired nutrition,* due especially to faulty appetite, and in healthy individuals who are *underweight.* The rationale of this procedure lies in the relationship between the level of blood sugar and the sensation of hunger. Many reports of marked gain in weight as the result of such therapy have appeared. The dosage commonly employed is 10 units three times daily, injected 20 to 30 minutes before mealtime. Evidence is contradictory as to whether the weight gained is retained after cessation of therapy.

Insulin has been extensively employed in the treatment of *schizophrenia.* Numerous favorable reports appear in the literature. The patients are given sufficiently large doses to produce "insulin shock." This drastic form of therapy apparently results in a remission of symptoms in a significantly high percentage of cases. The mechanism of action is unknown. Some consider it no different from that of metrazol convulsions. In this connection, it should be recalled that hypoglycemia markedly affects the central nervous system and diminishes its oxygen consumption. Thus Himwich and associates (1939) showed that during insulin-induced hypoglycemic coma, despite an adequate oxygenation of the blood, little oxygen is utilized by the brain. On the other hand, during and immediately after metrazol convulsions, the oxygen content of the blood is

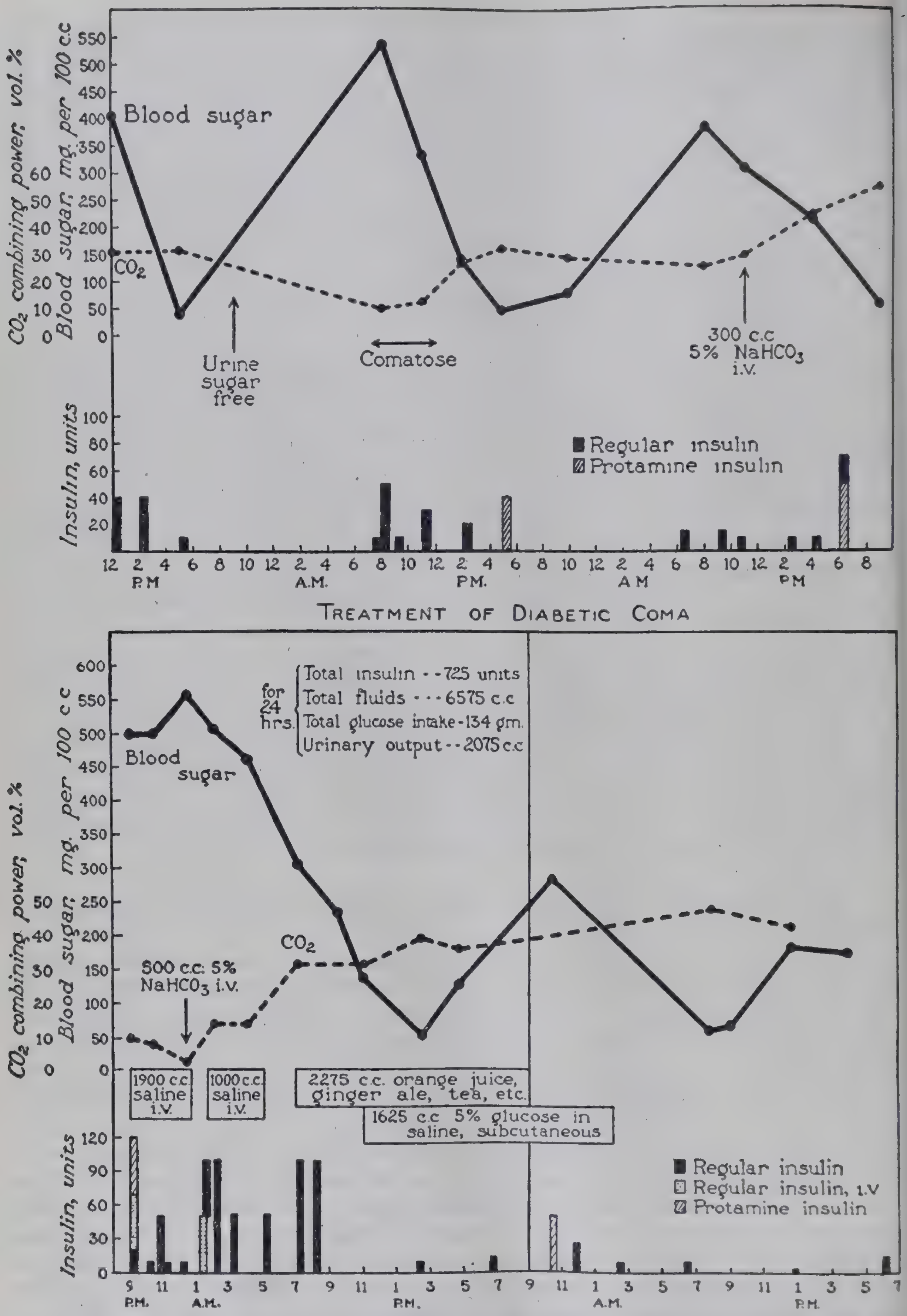

FIGURE 115. *The treatment of diabetic coma with special reference to the combined use of regular insulin and protamine zinc insulin.*

Two cases presented by Kepler, Ingham and Crisler (1937) not as models of perfection in treatment but rather to illustrate the difficulties which arise. *Upper:* Woman, aged 42, diabetic acidosis and coma precipitated by infection of finger. Regular insulin used for the first 30 markedly reduced and in this manner cerebral oxidations are impaired. Himwich and coworkers therefore believe that the mechanism of action of both insulin and metrazol in schizophrenia is associated with diminished cerebral metabolism. On this basis, they have treated schizophrenic patients with anoxia produced by the inhalation of nitrogen (Himwich and collaborators, 1938).

Treatment of schizophrenia with insulin requires experience, is not without danger, and the possibility of untoward late sequelae should not be overlooked. Prolonged hypoglycemia can cause irreparable damage to brain cells. Indeed, it has been suggested that cortical injury is the basis for the apparent improvement in schizophrenics. So many "cures" of schizophrenia have been endorsed enthusiastically only to be discarded after further study that one can hardly be criticized for viewing insulin therapy with caution.

Reports of the successful therapeutic action of insulin in the treatment of such divergent conditions as rickets, pellagra, peptic ulcer, circulatory disturbances, etc., should be viewed with skepticism unless one is convinced that there is some relationship between the pathological physiology of the disease being treated and the physiological mechanism of insulin action. It then remains to be proved that the latter is the basis of beneficial effects obtained.

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hours of therapy. Note the "escape from control" which occurred the first night after admission. Kepler and associates point out that more insulin should have been given at 10:00 P.M. despite the fact that the urine was sugar-free. The administration of protamine zinc insulin the following evening materially assisted the subsequent control of the patient's condition. Sodium bicarbonate was administered because the carbon dioxide combining power continued to hover at a critical level despite the fact that the glycosuria was controlled fairly well.

Lower: Woman, aged 30, classical diabetic acidosis and coma. Protamine zinc insulin administered on admission along with subcutaneous and intravenous insulin. Note the less stormy subsequent course as compared with the first case. Sodium bicarbonate was administered because the carbon dioxide combining power had dropped to the very alarming level of 2.26 volumes per cent. The unusually low requirement of insulin on the second day is probably attributable to the early use of protamine zinc insulin. Kepler and associates state that the patient should have received more regular insulin during the first few hours after admission. (After Kepler, Ingham and Crisler, 1937. Courtesy of the Division of Publications, Mayo Clinic.)

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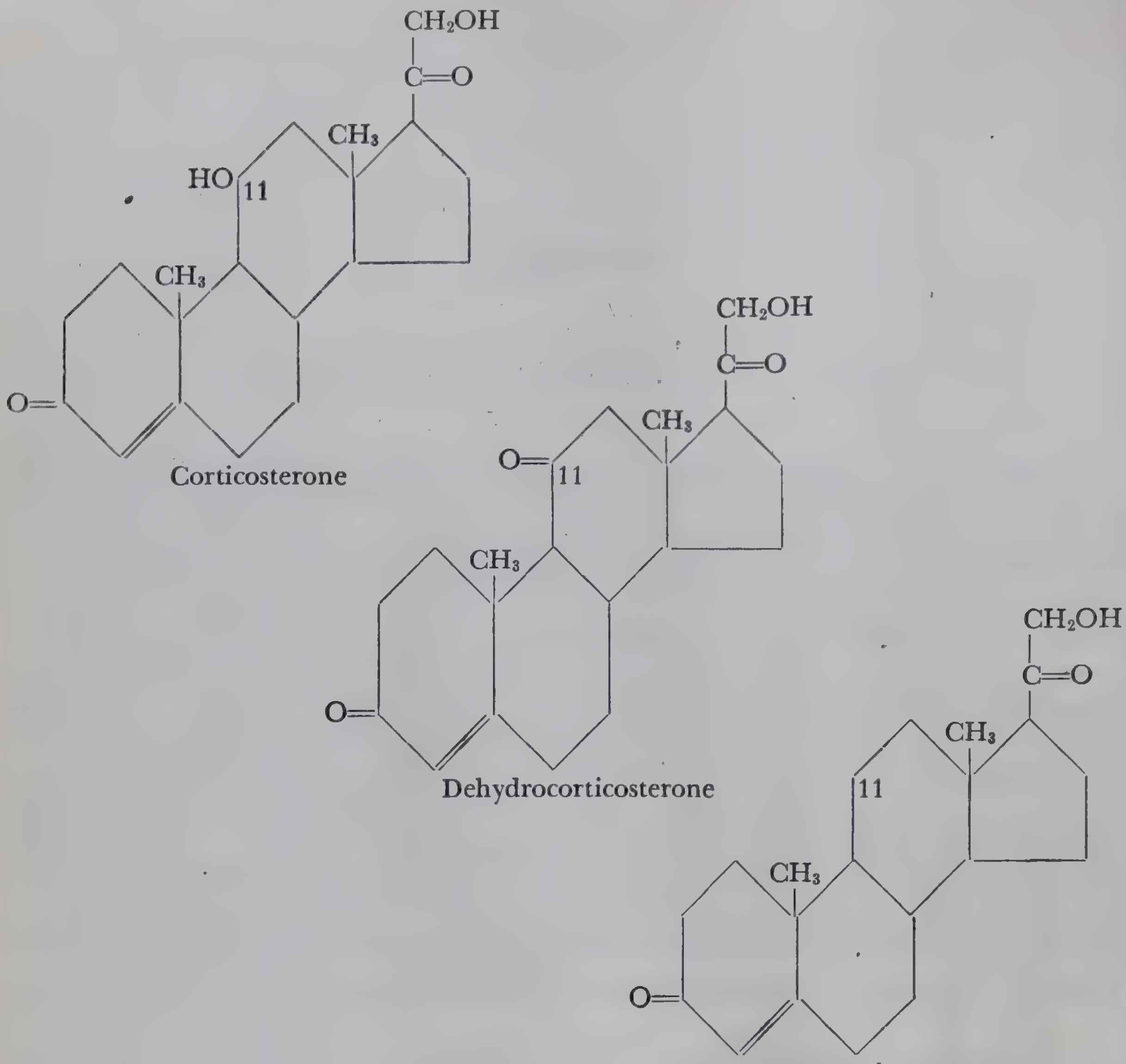
CHAPTER 69

ADRENAL CORTICAL HORMONES

History. The adrenal glands were apparently first described by Eustachius in the sixteenth century, and called by him the *glandulae renibus incumbentes.* However, various designations were later given by others, accounting for the dual English nomenclature of "suprarenal" and "adrenal" gland. The latter term is the more generally applicable because of the varied loci of the glands in different species. The early beliefs concerning the functions of the adrenals represented fanciful theories. To cite but two, it was postulated by Molinetti that the glands functioned during fetal life to draw blood from the kidney and prevent the formation of urine by the fetus, whereas Von Helmont believed that the adrenals secreted a substance which prevented the formation of renal calculi. The true importance of the adrenals was first appreciated only after Addison (1849, 1855) associated the disease which now bears his name with destructive lesions in the glands. His observations interested the physiologist Brown-Séquard who made the pioneer experiments establishing the adrenal glands as essential to life. Despite the vast amount of information which has accumulated since then, the essential function of the adrenal cortical hormone is still not definitely known.

Chemistry. Although it had long been suspected that the adrenal cortex possessed an endocrine function, it was not until 1927 that active extracts capable of prolonging the life of adrenalectomized animals were obtained. Since that year, rapid progress has been made toward the solution of the chemical nature of the adrenal cortical hormone. Methods of extraction and purification were improved and in 1934 Kendall and coworkers announced the isolation of a crystalline substance capable of maintaining the life of an adrenalectomized animal. Reichstein (1936, *et seq.*) and Wintersteiner and Pfiffner (1935, *et seq.*) have also obtained active crystalline preparations.

The chemistry of the active principle of the adrenal cortex resembles that of the sex hormones in several ways. There are numerous chemically related compounds, possibly a score or more, obtainable from the cortical tissue, most of which possess some degree of physiological activity, just as there are chemically related estrogens and androgens. There is a marked similarity in the chemical structure of the adrenal cortical and sex hormones, especially the androgens. Also the esterification of adrenal cortical hormones increases their potency and duration of action (Miescher and coworkers, 1938). Following are the structural formulas of three of the active compounds that have been isolated from the gland. Desoxycorticosterone is the most potent member of the group. Like estradiol, it was synthesized (Steiger and Reichstein, 1937) before it was isolated from its endocrine source (Reichstein and Euw, 1938). The close chemical relationship of the cortical hormones to testosterone is evident.



Corticosterone

Dehydrocorticosterone

Desoxycorticosterone

The chemistry of all the natural congeners of the adrenal cortical hormones is not completely solved. However, there is reason to believe that the chemical structure of the more active compounds, when finally determined, will not differ greatly from those presented.

Function of the Adrenal Cortex. Adrenal Insufficiency. Although there is no doubt that the adrenal cortex is essential to life, physiologists are uncertain of the rôle that this hormone plays in the mammalian organism. Attention has focused upon three types of disturbance which follow hypofunction or ablation of the gland. (1) There is a marked abnormality in the metabolism of sodium resulting in a negative balance of this ion, a fall in the total electrolyte content of the extracellular fluid and a resulting shift in the distribution of the body fluids. (2) There is an abrupt increase in the concentration of potassium in the extracellular fluids associated with a decreased renal excretion of this ion. (3) Carbohydrate metabolism is seriously altered as is evidenced by a diminished concentration of glucose in the blood and a greatly reduced glycogen content of liver and muscle. One might say that the adrenal cortex, like the anterior pituitary, secretes several hormones, and that this fact accounts for the manifold physiological changes which follow its removal. An alternative interpretation is that a single active crystalline cortical hormone can correct all aspects of the deficiency. This raises the problem of ascribing to the cortical hormone a basic function which can account for all the above disturbances in addition to many others which will be mentioned. Experimental evidence to solve this point is not yet decisive. The problem will be discussed more completely after the various features of adrenal insufficiency and hormonal action have been presented.

Sodium Loss. There is little doubt that many of the symptoms of adrenal insufficiency are related to a disturbance in sodium metabolism. In both patients and most species of experimental animals there is a reduction in the concentration of serum sodium (Figure 116). The loss of sodium is probably the result of renal insufficiency, the kidney failing to reabsorb a sufficient quantity of this essential

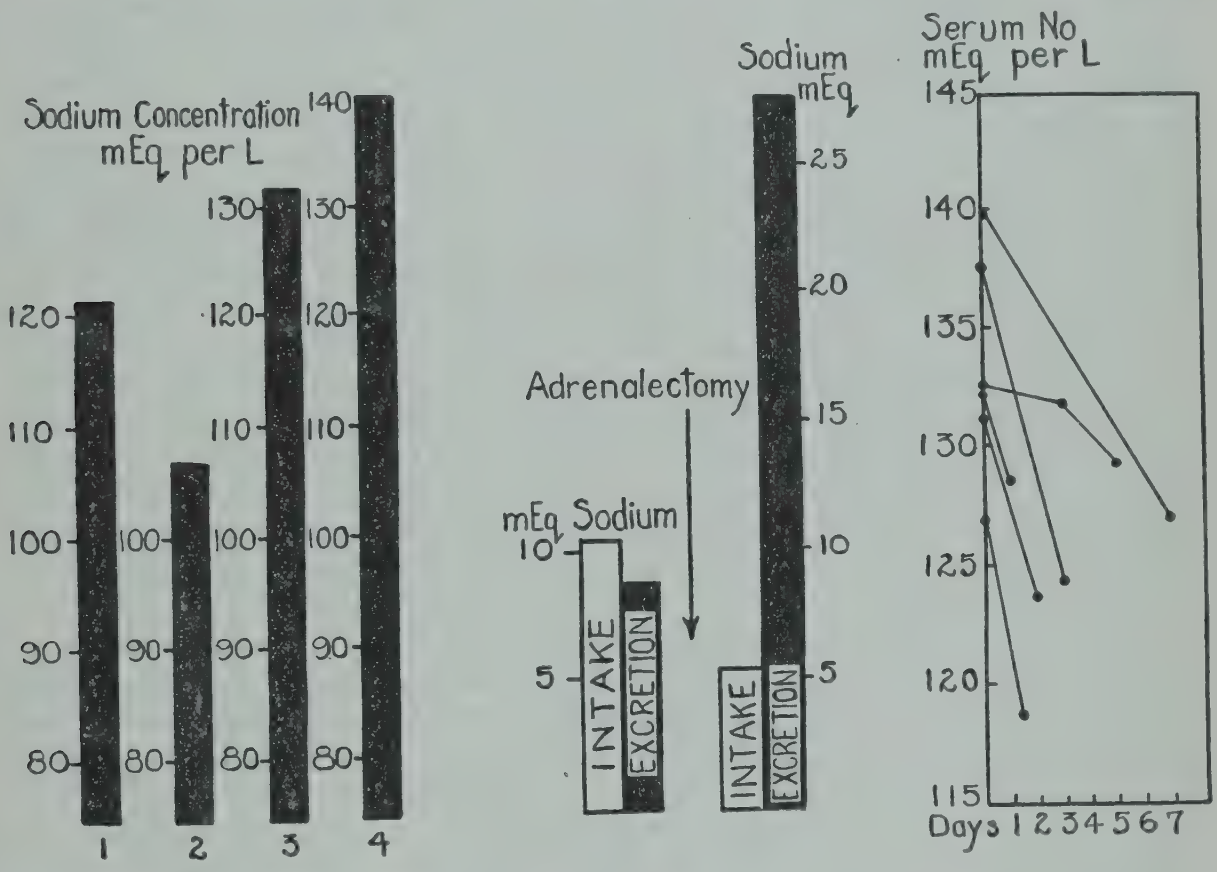


FIGURE 116. *The rôle of sodium in adrenal insufficiency.*

Left: The relation of symptoms to the concentration of serum sodium in Addison's disease. 1. Before the administration of sodium chloride, the patient was weak, nauseated and vomiting. 2. The serum sodium continued to fall to an unusually low level, and the patient became moribund. 3. Sodium chloride (15 grams daily) was administered for one week and the patient regained sufficient strength to walk about the ward. 4. With continued salt therapy, the concentration of serum sodium rose to normal and the patient was able to remain at home and do most of her housework.

Center: The effect of adrenalectomy in the dog on the excretion of sodium. After removal of the adrenal glands, large amounts of sodium are lost through the kidney, resulting in a markedly negative sodium balance. This condition is reflected in a fall in the concentration of sodium in the extracellular fluid.

Right: The effect on the concentration of serum sodium of withdrawal of sodium chloride from the diet of patients with Addison's disease. Each line represents a different patient. Regardless of the initial value, the serum sodium falls precipitously. No such fall is observed when sodium chloride intake is restricted in normal individuals, or those with miscellaneous diseases. Accompanying the fall in serum sodium, symptoms of profound weakness, prostration, and nausea and vomiting develop in from one to five days. This procedure is of diagnostic value but may be dangerous. (After Loeb, Atchley and Stahl, 1935. Courtesy of *The Journal of the American Medical Association.*)

cation to maintain the normal osmotic pressure of the extracellular fluid (Harrison and Darrow, 1939). With a fall in the concentration of extracellular electrolyte, the extracellular fluids become hypotonic to the intracellular and consequently there is a shift of water into the cells. The mechanism of this water shift is the same as that which occurs with other types of sodium loss and is described in detail in connection with the pharmacology of the sodium ion (page 589). The water shift results in anhydremia which is characterized by an increase in the concentration of plasma protein, hemoglobin and oxygen capacity, and a decrease in plasma volume, rate of blood flow and blood pressure. As the anhydremia progresses renal function is further impaired, and retention of urea, sulfate and phosphate occurs. Eventually, severe shock intervenes.

In this discussion, primary emphasis has been placed upon the decreased sodium concentration of the extracellular fluid as the cause of the marked disturbance in the distribution of body fluids. However, there is evidence to suggest that the adrenal hormone may exert a more selective action on the distribution of body fluids than that indirectly produced by a loss of sodium. For example, Swingle has repeatedly emphasized that experimental animals can recover from all the symptoms of shock after adrenalectomy merely by the administration of cortical hormone without the replacement of the lost sodium. He believes that the cortical hormone is concerned with the maintenance of capillary tone and in this manner controls the volume capacity of the circulatory system (Swingle and associates, 1938). Also, Britton and Silvette (1937) have shown that in certain species adrenalectomy causes the symptoms of adrenal insufficiency without attending disturbance in the electrolyte metabolism. In the rat, Harrison and Darrow (1938) failed to find a correlation between the severity of deficiency symptoms and disturbance in the sodium concentration of the blood. Lastly, clinical symptoms can be severe at a time when the chemistry of the patient's blood is only moderately distorted (Loeb, 1939).

On the other hand, it has been repeatedly demonstrated that adrenalectomized animals survive over extended periods of time without hormonal replacement therapy if large amounts of sodium salts are provided. Also, the maintenance dose of hormone for human beings with Addison's disease can be materially reduced if large amounts of sodium salts are included in the diet. In fact, hormonal therapy may not be necessary in many cases if the sodium content of the diet is sufficiently high. Lastly, in the event that sodium is removed from the diet of a patient with a mild degree of cortical deficiency there is a marked exacerbation of symptoms (Figure 116). The procedure of sodium withdrawal may be employed as a diagnostic test. If, within seven days, symptoms become more severe and the serum sodium concentration falls more than four mEq per liter, the diagnosis of Addison's disease seems likely (Loeb, 1939).

Potassium Retention. Following extirpation of the adrenals, there is a steady increase in the potassium level of the blood and extracellular fluids (Truszkowski and Zwemer, 1936; Wilder and associates, 1937). The concentration of cellular potassium in certain tissues, notably muscle, also rises (Darrow, Harrison and Taffel, 1939). The extracellular concentration of the ion becomes sufficiently elevated to warrant the consideration of potassium as a possible cause of many of the symptoms of adrenal cortical insufficiency. The toxic actions of the potassium ion are presented elsewhere. Seemingly, the retention of potassium is due to a functional renal defect, for ordinarily the kidney can excrete this cation with sufficient celerity to prevent its accumulation in the blood stream even when very large amounts are administered. Thus, in adrenal cortical insufficiency there is a dual disturbance in the renal excretion of electrolyte. Sodium, which is normally reabsorbed in order to maintain osmotic equilibrium, is lost in excess amounts. On the other hand, potassium, which is normally excreted, is retained (Figure 117). It is possible that the kidney has lost the ability to differentiate between these chemically similar but physiologically different cations. That some of the symptoms of adrenal cortical insufficiency are due to the high concentration of potassium in the extracellular fluid appears probable. If a patient with Addison's disease is placed upon a low potassium diet his symptoms improve, whereas if large amounts of potassium are ingested his condition becomes definitely worse. Indeed, a measurement of potassium tolerance has been employed as a diagnostic test in Addison's disease.

Carbohydrate Metabolism. Some aspects of the relation between the adrenal cortex and carbohydrate metabolism are discussed under the pharmacology of insulin. There is apparently some type of antagonistic action between the two hormones. Cortical extracts increase the severity of the diabetic state in partially depancreatized animals probably by increasing the rate of gluconeogenesis (see below). In a high percentage of adrenalectomized animals and in many cases of clinical adrenal cortical insufficiency the concentrations of blood sugar and liver and muscle glycogen are markedly reduced. Likewise, patients with Addison's disease are quite sensitive to insulin. Britton is of the opinion that abnormalities in carbohydrate metabolism represent the primary disturbance in adrenal insufficiency and are the reason for the fatal outcome (Britton and coworkers, 1932, 1933, 1937, 1938). Opposed to this view is the fact that hypoglycemia is not a constant finding in severe adrenal cortical insufficiency and also that the administration of glucose will not greatly prolong the life of an adrenalectomized animal. Nevertheless it seems evident that any comprehensive theory of the mechanism of adrenal cortical function must take into account the profound disturbances in carbohydrate metabolism which exist after removal of the gland and the effects of the injection of the hormones of the adrenal cortex on the metabolism of sugars.

There is some evidence that the disturbance in carbohydrate metabolism noted in adrenalectomized animals is closely related to the abnormalities in potassium metabolism. For example, Kendall (1938) observed that when adrenal cortical extract is administered to partially depancreatized rats not only does a glycosuria result but also the potassium excretion may be enhanced as much as tenfold. He also noted that the administration of potassium increased glycosuria. In this connection, Silvette, Britton and Kline (1938) reported that the injection of potassium raises the level of blood sugar and depletes the tissues of glycogen. It remains to be determined, however, whether these changes are specific effects of potassium (page 597).

Adynamia. Muscle weakness is one of the prominent symptoms of adrenal cortical insufficiency. It is evident in smooth as well as in skeletal muscles. Adynamia may be due to the impaired circulation, or, on the other hand, it may result from a fundamental disturbance in the metabolism of muscle tissue. The injection of cortical extract in normal human beings slightly increases the efficiency of muscle during light exercise (Hitchcock, Grubbs and Hartman, 1938; Missiuro, Dill and Edwards, 1938).

Temperature Regulation. The ability of the adrenalectomized animal to regulate body temperature is markedly impaired. Adequate adjustment cannot be made either to excessive heat or cold. This is probably due to a primary disturbance in the circulation. The symptoms of mild Addison's disease are often exaggerated by hot weather. It is likely that the additional loss of sodium and fluid incident to sweating produces a severe strain on a relatively inefficient circulation.

Pigmentation. In clinical adrenal insufficiency the patients become characteristically bronzed in color. Little is known of the mechanism of the pigmentary change and it is not observed in experimental animals. It is only partially removed by hormonal therapy.

Effects of Cortical Hormone on Adrenal Insufficiency. When the adrenal cortical hormones are injected into adrenalectomized animals or patients with

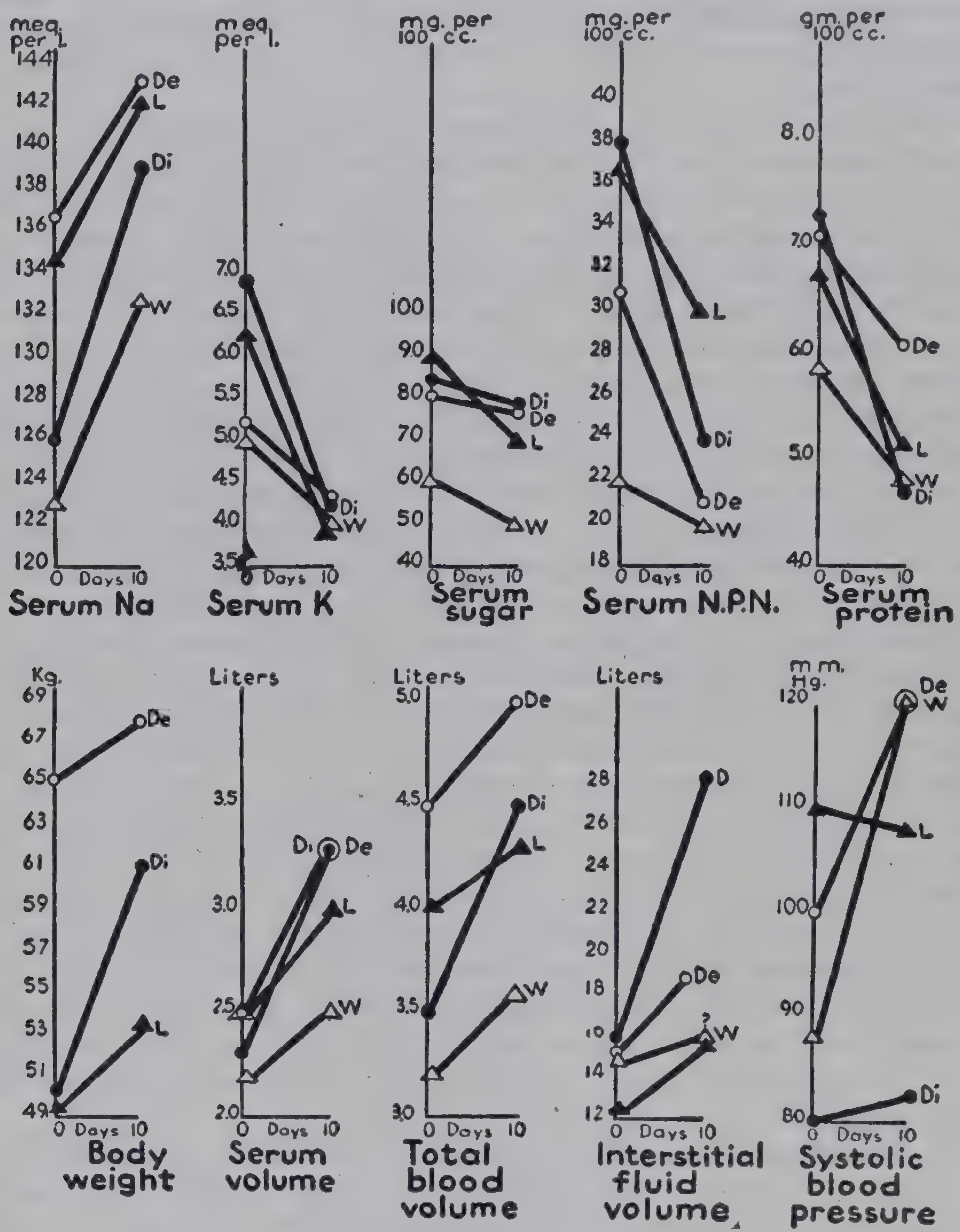


FIGURE 117. *The effects of desoxycorticosterone on the composition of the blood of patients with Addison's disease* (see text). (After Ferrebee, Ragan, Atchley and Loeb, 1939. Courtesy of *The Journal of the American Medical Association.*)

Addison's disease all the changes described can be reversed. The concentration of serum sodium rises and this in turn leads to an increase in the volume of plasma and extracellular fluid and a decrease in the concentration of protein and cellular elements of the blood. There is usually a concomitant rise in blood pressure. The concentration of serum potassium falls. Renal function improves, and if elevated the blood levels of N.P.N. and phosphate return to normal. Body weight increases and muscular strength improves. Little change in pigmentation occurs, however.

The effects cited are depicted in Figure 117. (*See* Ferrebee and coworkers, 1939; Thorn and associates, 1939.)

Hyperfunction of the Adrenal Cortex. Comparatively little is known concerning the action of excess amounts of adrenocortical hormone. One clinical condition associated with hyperfunction of the adrenal cortex is Cushing's disease (page 1184). In fact it is believed by some that adrenal cortical hyperplasia is a more constant finding in this syndrome than is pituitary basophilism, and many symptoms of the disease may be directly due to adrenocortical hyperfunction (Anderson and coworkers, 1938). There seems to be little doubt that the masculinization of females and the feminization of males may be associated with excessive cortical secretion. The close chemical relationship between the cortical hormones, estrogens and androgens supports this view. It may be recalled here that following castration in the male the urine still possesses some androgenic activity. The source of this active substance is probably the adrenal cortex. Also, the androgenic activity of the urine of females is believed to be due to the excretion of a principle originating in the adrenal cortex. The androgenic activity

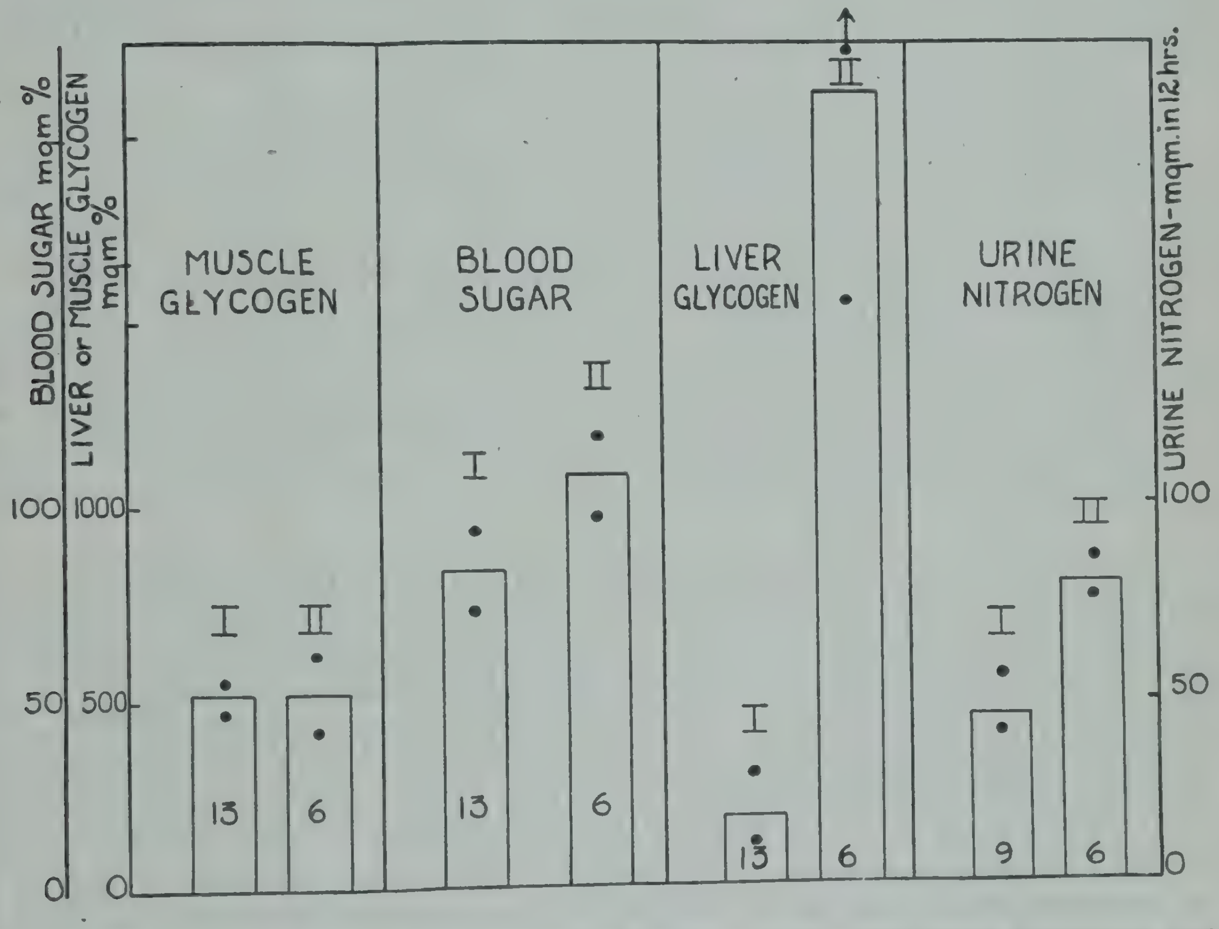


FIGURE 118. *The effect of adrenal cortical extract on the carbohydrate metabolism and nitrogen excretion of fasted normal rats.*

I, uninjected controls; II, rats receiving cortical extract. The figures in the vertical columns indicate the number of experimental animals in each group. The height of the columns represents the average value for the group, and the black dots show the maximal deviation from this average. Note the great increase in liver glycogen after injection of cortical extract. The increased excretion of urinary nitrogen is of sufficient magnitude to suggest that protein was the source of the deposited glycogen. The muscle glycogen is not significantly altered and the blood sugar is only moderately elevated. (After Long, 1939. Courtesy of the *Transactions and Studies of the College of Physicians of Philadelphia.*)

of desoxycorticosterone has been estimated to be 1/30 that of androsterone (Hooker and Collins, 1940). An outstanding case of virilism due to an adrenal cortical tumor has been presented by Lukens and Palmer (1940).

Effects of Cortical Hormones on Normal Animals. In view of the marked changes in the metabolism of electrolytes after the extirpation of the adrenals, one would expect the opposite effects to follow injection of excessive amounts of active extracts. A retention of sodium and an increased elimination of potassium have been demonstrated in normal human beings and in dogs receiving active extracts (Harrop and Thorn, 1937; Hartman and coworkers, 1938; Thorn and associates, 1937, 1938). These changes, however, are not marked and are difficult to detect. It is also of interest that similar effects on sodium and potassium can be observed after the administration of the chemically related sex hormones (Thorn and Engel, 1938).

The administration of pure desoxycorticosterone in large doses to normal animals, however, causes more striking changes. Kuhlmann and associates (1939) injected dogs with 20 to 25 mgm of desoxycorticosterone acetate and observed a slight increase in the concentration of extracellular sodium and a marked reduction in serum potassium, the normal blood content being halved. Accompanying the loss of potassium there was marked muscular weakness. The rôle of potassium in neuromuscular physiology is discussed on page 596.

The injection of the active principles of the adrenal cortex causes striking changes in carbohydrate metabolism. The early contention of Britton and Silvette (1932) that extracts of the adrenal cortex elevate the carbohydrate stores of adrenalectomized animals above the normal limits has been amply confirmed. Indeed, adrenal cortical hormone, when given to normal fasting rats, causes an increase in the concentration of blood sugar and a marked deposition of liver glycogen. Accompanying this action there is an increase in the excretion of urinary nitrogen indicating that the source of the carbohydrate is from protein (Long, 1939; Long, Katzin and Fry, 1940). Adrenal cortical hormone can also raise the blood sugar and increase the glycogen reserve of the liver of hypophysectomized rats (Long and Katzin, 1938) (Figure 118).

Relation Between Chemical Structure and Hormonal Activity. Mention has already been made of the problem whether a single adrenal cortical hormone can correct the various physiological deficiencies which follow adrenalectomy. On the basis of experimental evidence the answer to this question remains equivocal. The following facts can be stated. A single crystalline compound, such as desoxycorticosterone, is capable of maintaining the life of adrenalectomized animals and patients with Addison's disease. Other crystalline preparations of different chemical composition are much less active in this regard, adrenalectomized animals requiring a higher maintenance dose. Desoxycorticosterone is much more effective in correcting the defect in electrolyte metabolism than it is in promoting gluconeogenesis (Wells, 1940) or relieving adynamia (Ingle, 1940). The opposite is true of corticosterone. The ability of cortical hormones to maintain life seemingly is related to their effect on electrolyte metabolism. Nevertheless, there is evidence that patients with Addison's disease maintained on crystalline desoxycorticosterone show further clinical improvement if given supplemental therapy with an extract of the adrenal cortex which probably contains several principles closely related chemically (McCullagh and Ryan, 1940). Lastly, there are compounds intermediate between desoxycorticosterone and corticosterone which seemingly possess all types of activity mentioned to a moderate degree. To further complicate the problem it may again be stated that the pigmentation characteristic of Addison's disease persists despite any type of therapy, although it may recede to some extent.

The chemical configuration which apparently largely determines the predominant actions of a particular crystalline preparation from the adrenal cortex is the presence or absence of oxygen on carbon 11. When oxygen is absent the predominant action is on electrolyte metabolism; when oxygen is present, on carbohydrate and muscle metabolism (Kendall, 1940).

Bio-assay. There is no standard method for the bio-assay of adrenocortical preparations. Several procedures are employed. Most preparations are assayed for their ability to maintain the life of adrenalectomized animals. Dogs and rats are the two species commonly used. Other bio-assay methods take advantage of the ability of the hormone to allay muscular fatigue in adrenalectomized animals or to promote the renal reabsorption of sodium in normal experimental subjects.

Absorption and Excretion. Cortical hormone can be absorbed from the gastro-intestinal tract but some activity is lost when this route is employed. In the clinical use of the cortical hormone, parenteral administration is usually used. Thorn and associates (1939) have successfully treated patients with Addison's disease with pellets of crystalline hormone implanted subcutaneously. Little is known of the intermediary metabolism and excretion of the hormone. Seemingly it is rapidly eliminated, for deficiency symptoms can be detected in experimental animals within 24 to 48 hours following cessation of hormone therapy.

Preparations. Several commercial preparations of the cortical hormone are available. These take the form of glandular concentrates or crystalline preparations of desoxycorticosterone. None is official or accepted for inclusion in N.N.R. The clinical value of the various glandular concentrates should be determined by trial, because there is no standard method of assay and only by experience can one learn the worth of a particular product. Crystalline desoxycorticosterone acetate is marketed in oily solution for intramuscular injection.

Therapeutic Uses. The specific therapeutic use for the hormones of the adrenal cortex is in the treatment of *Addison's disease*. Within the decade between the isolation of the first active concentrates of the adrenal cortex and the introduction into therapy of crystalline compounds possessing hormonal activity, the ease and efficacy of treatment have steadily increased so that at present the patient with Addison's disease can usually lead an ambulatory and useful life and be only slightly inconvenienced by his therapeutic regimen. What is more the cost of therapy has been reduced to a few dollars a week.

Before desoxycorticosterone was available for the therapy of Addison's disease, treatment centered around the parenteral use of adrenal cortical extracts. The commercial preparations varied in activity, and even the most potent material was relatively ineffective unless supplemental measures were employed. These consisted mainly of a restriction in the intake of potassium (*see* Wilder and associates, 1937) and an increase in the intake of sodium. The maintenance dose of cortical extract usually ranged from five to 10 cc intramuscularly and an extradietary intake of 10 grams of sodium chloride was recommended.

The availability of desoxycorticosterone has relegated the use of cortical extracts to secondary importance. With a crystalline preparation of known activity obtainable, therapy can be placed upon a quantitative basis. What is more, desoxycorticosterone is more potent and effective, especially in regard to its effect on electrolyte metabolism, than is cortical extract. While this has removed some problems in therapy it has created others.

Seemingly the action of desoxycorticosterone to maintain the life of patients with Addison's disease is based upon its ability to correct the existing defect in electrolyte metabolism. Presumably the site of action of the compound is on the renal tubule; the mechanism of action is to restore the ability of the tubules to reabsorb sodium salts and to excrete potassium. Normally the extent of reabsorption of sodium is delicately adjusted by the kidney so that a sodium balance is maintained. Inasmuch as the amount of retained sodium largely determines the volume of extracellular fluid (page 580), it follows that the regulatory action of the kidney in the rejection or reabsorption of sodium is the mechanism by which the body maintains a relatively constant extracellular fluid volume. When a potent agent such as desoxycorticosterone is employed to stimulate the reabsorption of sodium salts by the kidney, this regulatory action is lost. If the dose of desoxycorticosterone is too high, or the sodium intake too large, the resulting reabsorption of extracellular electrolytes and fluid will be so great as to tax the capacity of the

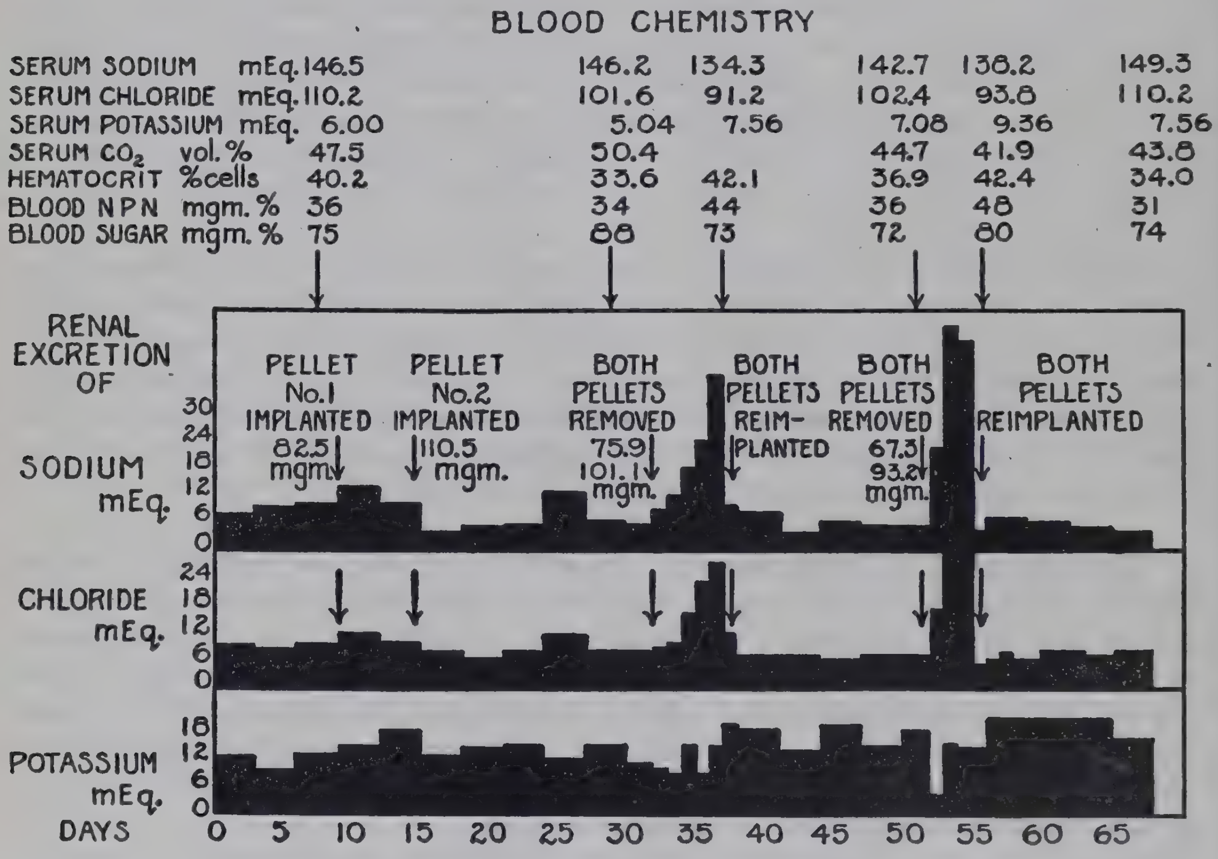


FIGURE 119. *The treatment of experimental adrenal insufficiency by the subcutaneous implantation of pellets of crystalline desoxycorticosterone acetate.*

Bilaterally adrenalectomized dog sustained by the daily injection of 1.5 mgm of desoxycorticosterone acetate in oil. Following the cessation of these injections, the implantation of a single pellet of the hormone (82.5 mgm) failed to maintain the animal. Rapid improvement followed the implantation of a second pellet (110.5 mgm). Adrenal insufficiency could be produced at will by the removal of the pellets and recovery rapidly obtained by reimplantation of the hormone. Observe the slow utilization of the hormone as indicated by the gradual decrease in the weight of the pellets. Note the increase in the urinary excretion of sodium and chloride and the decrease in the elimination of potassium which immediately follow the removal of the hormone. The changes in renal function are clearly reflected in the blood chemistry. (After Thorn, Engel and Eisenberg, 1939. Courtesy of the *Bulletin of The Johns Hopkins Hospital.*)

extracellular fluid reservoir. The result is edema formation, an increased circulating blood volume possibly accompanied by hypertension, and, if precipitating factors exist, acute circulatory failure with sudden death. Before the potency of the action of desoxycorticosterone on the kidney was fully appreciated, several deaths resulted from the combined use of the hormone and sodium chloride (Ferrebee and associates, 1939; Wilder, 1940).

Desoxycorticosterone does not correct the defect in carbohydrate metabolism, which is evident to a variable degree in patients with Addison's disease. The possibility has been entertained that some of the deaths associated with the use of desoxycorticosterone may have been due to hypoglycemia (Wilder, 1940; Thorn and Firor, 1940).

Therapy of *Addison's disease* with desoxycorticosterone centers around striking a balance between the dose of hormone and the intake of salt. The routine recommended by Thorn and Firor (1940) is to start treatment with the daily intramuscular injection of two to five mgm of desoxycorticosterone acetate in oil supplemented by the oral ingestion of six to eight grams of sodium chloride. Too rapid gain in weight (more than 0.5 kg daily during the first week of treatment and more than 0.3 kg daily subsequently) indicates overdosage and demands either a reduction in the dose of hormone or in salt intake. Each patient must be adjusted individually. The optimum daily maintenance dose of desoxycorticosterone is one which will maintain body weight without the appearance of edema or too great an elevation in blood pressure. The diet should be high in readily available carbohydrate.

In treating a patient in an *Addisonian crisis,* more heroic measures are needed. In this instance large amounts of sodium have already been lost from the body, the patient is not ingesting food, and large amounts of sodium and glucose in addition to cortical hormone must be given. The routine suggested by Thorn and Firor (1940) consists in the administration of massive doses of desoxycorticosterone acetate in oil by intramuscular injection (25 to 35 mgm on the first day plus 25 cc of cortical extract subcutaneously; 10 to 20 mgm on the second; five to 10 on the third) plus the daily intravenous injection of saline and dextrose. Sodium chloride and glucose are given as follows: upon admission, 1000 cc of 1.5 per cent sodium chloride solution containing 25 cc of cortical extract and 1000 cc of five to 10 per cent glucose solution; after 12 and 24 hours, 1000 cc each of isotonic sodium chloride and glucose solutions; on the third day, three to six grams of sodium chloride are given by mouth. The patient is observed closely for signs of edema formation or hypoglycemia.

The subcutaneous implantation of crystalline pellets of desoxycorticosterone has proven to be an effective and convenient method for controlling patients with Addison's disease (Thorn and associates, 1939; Thorn and Firor, 1940). The pellets, weighing between 100 and 150 mgm each, are implanted in the infrascapular region. The maintenance dose of the patient is first determined with the use of intramuscular injections of desoxycorticosterone acetate in oil. One pellet is then implanted for each 0.4 to 0.5 mgm of desoxycorticosterone required by the intramuscular route. A single implantation of pellets should be effective for nine to 12 months. The therapeutic use of pellets in adrenalectomized dogs is depicted in Figure 119.

Tooke and coworkers (1940) have shown that a patient with Addison's disease who is treated with desoxycorticosterone is not adversely affected by a generous intake of potassium. What is more, a liberal intake of potassium has the tendency to counteract the retention of an excessive amount of sodium. Conversely the restriction of dietary potassium favors the retention of sodium.

Desoxycorticosterone has been recommended for the *prophylaxis and treatment of surgical shock.* For the prophylaxis of shock it has been suggested that patients be given large amounts of sodium chloride solution and desoxycorticosterone for several days prior to operation. Undoubtedly this would serve to increase the circulatory blood volume inasmuch as large amounts of salt and fluid would be retained; but whether such a procedure would be effective in preventing the onset of shock, considering the pathological physiology of this condition (page 586), is open to question. What is more, there is the real danger of overtaxing the circulatory system. As a therapeutic measure in the treatment of preexisting shock, theoretical considerations do not support the validity of this procedure. Although the objective of therapy is to increase the blood volume, desoxycorticosterone accomplishes this by a renal mechanism. Shock is usually associated with anuria, and the problem involved is not the loss of circulating fluid through the kidney but rather through widely dilated capillaries. Until it has been more definitely shown that there is an element of capillary action in the effect of adrenal cortical hormones on the distribution of body fluids, there is little physiological basis to the use of desoxycorticosterone in the treatment of shock. Clinical evidence is as yet too meager to warrant a definite conclusion that desoxycorticosterone is of value.

The use of adrenal cortical hormones has been recommended in the treatment of numerous other conditions unassociated with adrenal insufficiency. In no instance is therapy sufficiently rational or are therapeutic results sufficiently convincing to warrant discussion.

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SECTION XVI

THE VITAMINS

The British Medical Research Committee in 1919 published a review entitled, "Report on the Present State of Knowledge Concerning Accessory Food Factors (Vitamines)." In this report the following statement was made, "Disease is so generally associated with positive agents—the parasite, the toxin, *the materies morbi*—that the thought of the pathologist turns naturally to such positive associations and seems to believe with difficulty in causation prefixed by a *minus* sign." A statement of the present status of vitamins as drugs may be worded in almost an identical manner. The action of drugs is so generally associated with positive responses—stimulation or depression—that the thought of the physician turns naturally to such positive associations and seems to believe with difficulty that normal constituents of the diet are valuable and widely applicable therapeutic agents.

The classification of vitamins merely as accessory food factors no longer takes cognizance of the rapid advance in our knowledge of the chemistry and pharmacological activity of these substances. From unknown dietary constituents, vitamins have evolved into definite chemical entities with marked physiological and therapeutic activity. As such they deserve recognition and consideration as drugs.

Until recently, vitamin deficiency was considered a phenomenon observed in experimental animals fed bizarre diets, or a syndrome prevalent only in countries where the choice of foods was extremely limited. At present, however, it is recognized that vitamin deficiencies are widespread in occurrence and that subclinical deficiencies which warrant specific therapy with vitamins are still more prevalent. Also it has become evident that certain events may contribute to a vitamin deficiency in the face of a normally adequate diet. These are the increased requirements during periods of rapid growth, pregnancy, infections and fever, vomiting or diarrhea, and impaired gastro-intestinal function. In addition, the metabolism of vitamins may be altered and abnormal storage, destruction and utilization may occur. Also, the possibility of a true dietary deficiency is ever present, the chief contributing causes of which are poverty and food fads.

In the past, vitamin therapy consisted in the use of food substances rich in the particular vitamin required. At present, with the availability of crystalline preparations or highly potent concentrates of all the vitamins of clinical interest, it is possible to give exact doses of the particular agent desired in a pure form. The availability of potent vitamin preparations has greatly enhanced the clinical knowledge of vitamins. For one thing, it has allowed specific therapy of deficiency syndromes and the therapeutic evaluation of pure preparations. With the elucidation of the chemical structure of vitamins, it has been possible in some instances actually to determine the vitamin concentration in the blood and tissues and thus use a chemical approach to the diagnosis of nutritional deficiency.

The availability of vitamin concentrates has also led to abuses. One of these is the compounding of vitamins in expensive mixtures which could not possibly have a rational therapeutic use. This so-called "shot-gun" vitamin therapy has been soundly condemned by the Council on Pharmacy and Chemistry (1937, 1939). The specific use of vitamins is in the treatment of the deficiency syndromes. Their therapeutic value in such states has been adequately proved. There is a growing tendency, however, to prescribe vitamins for those conditions which simulate certain aspects of nutritional disease, but which have an entirely different etiology. For example, since scurvy which is due to vitamin C deficiency is characterized by an increased capillary fragility, vitamin C has been used in the treatment of such blood dyscrasias as thrombocytopenic purpura, leukemia, hemophilia, etc. Likewise vitamin A is indiscriminately employed in all types of infection, and thiamine in a variety of conditions characterized by peripheral neuritis. At present there is no clear-cut evidence which indicates that the vitamins are of therapeutic value in diseases uncomplicated by some degree of vitamin deficiency.

The acceptance of vitamins as drugs requires that they be employed as drugs. This necessitates a knowledge of their pharmacodynamic properties, their physiological actions, and their therapeutic indications and uses. It is difficult, in discussing a subject as broad as the vitamins sharply to define what constitutes their pharmacology. The material presented will therefore be limited to a discussion of their chemistry, pharmacological actions, physiological functions, clinical manifestations of vitamin deficiency, absorption, fate and excretion, bio-assay and unitage, available preparations, human requirements, and therapeutic indications and uses.

CHAPTER 70

WATER-SOLUBLE VITAMINS

I. THE VITAMIN B COMPLEX
THIAMINE, RIBOFLAVIN, NICOTINIC ACID AND VITAMIN B_6

THE VITAMIN B COMPLEX

The resolution of the vitamin B complex into its individual constituents and the chemical identification of those components which are essential in human nutrition comprise one of the outstanding accomplishments of cooperative research.

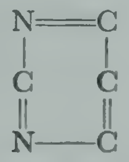
The so-called vitamin B was one of the first of the dietary essentials to be recognized, and the preparation from rice polishings (Funk, 1911) of a water-soluble concentrate active in the cure of beriberi was an important contribution not only to the chemistry of vitamin B but to the establishment of the concept of deficiency disease. The term "water-soluble B" was introduced by McCollum and Kennedy (1916) to describe that dietary substance necessary for growth in rats and seemingly essential for the prevention of beriberi. It soon became evident, however, that vitamin B was a complex rather than a single entity. The many investigations which have separated the vitamin B complex into its several constituents have been summarized by Nelson (1938). Of the multiple factors isolated in comparatively pure form, three are undoubtedly essential in human nutrition, and have not only been chemically identified but have also been synthesized. Therefore, with all question as to chemical composition removed, these three substances will be designated in the following discussion by their chemical names, thus avoiding the confusion caused by the many conflicting terms hitherto applied to components of the vitamin B complex.

The chemical entities of the vitamin B complex known to be essential in human nutrition are *thiamine* (vitamin B, vitamin B_1), *riboflavin* (vitamin G, vitamin B_2), *nicotinic acid* and possibly *vitamin* B_6. The other possible components, the significance of which in human nutrition has yet to be established, will not be considered.

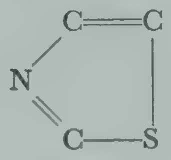
THIAMINE (VITAMIN B_1)

Chemistry. Thiamine is the name adopted by the Council on Pharmacy and Chemistry for crystalline Vitamin B_1 chloride. The elucidation of the chemical structure of thiamine was the end-result of 30 years of intensive research. Certain chemical and physical properties of the vitamin were described as early as 1906, but it was not until 1936 that its structure was established. Thiamine was first isolated in comparatively pure crystalline form by Jansen and Donath (1926), but the amount obtained was insufficient to ascertain its exact chemical composition. Windaus and associates (1932) established the correct empirical formula for the vitamin. In 1936, Williams announced its structure, which he verified by synthesis in the same year (Williams and Cline, 1936).

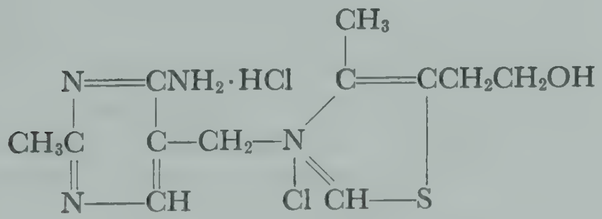
Thiamine is a complex organic molecule containing a pyrimidine and thiazole nucleus. The pyrimidine structure is common in nature, but the thiazole nucleus is unique, appearing, so far as is known, only in thiamine. The structures of thiamine chloride and its two component nuclei are as follows:



Pyrimidine



Thiazole



Thiamine Hydrochloride

The synthesis of thiamine has opened new therapeutic fields, for it has made this substance available at a reasonable cost. Moreover, chemical interest naturally centers on the relationship between changes in the thiamine molecule and alterations in physiological activity. Preliminary investigations on this relationship have been summarized by Williams and Spies (1938).

Pharmacological Actions. The availability of synthetic thiamine has permitted a study of its pharmacological properties, but most of the experiments have been concerned with the effect of very large doses. The symptoms observed may therefore be entirely unrelated to the actions of thiamine as a vitamin and probably represent only the untoward responses which follow the injection of excessive amounts of many organic compounds.

The toxic intravenous doses of thiamine for various species have been determined. These range from 125 mgm per kg for the rat to 350 mgm per kg for the dog. The toxic oral dose is approximately 40 times as great as the intravenous. The symptoms observed following the administration of toxic amounts of thiamine consist of weakness, tetany, labored breathing and death from respiratory failure. Daily intravenous injection of subtoxic doses leads to no cumulative action. Toxic doses of thiamine are many thousand times greater than the therapeutic, and thus the vitamin has a very high therapeutic index. There is no reason to expect untoward reactions from even the most vigorous therapeutic regimen with thiamine.

Aside from the responses to toxic amounts, thiamine causes few other pharmacological reactions. There may be a slight vasodilatation and fall in blood pressure accompanying rapid intravenous injection, but this is transitory. Even large doses have no effect on the blood sugar level despite the fact that the physiological rôle of the vitamin is concerned with the intermediary metabolism of carbohydrates.

Absorption, Fate and Excretion. Thiamine readily gains access to the circulation from all sites of administration. It is almost quantitatively absorbed from the normal gastro-intestinal tract, and is stored in the body to a limited extent. All the tissues contain thiamine, but the highest concentrations are found in the liver, brain, kidney and heart. There are also appreciable amounts in skeletal muscle, spleen and lung. The extent of storage depends upon the level of vitamin intake. If the intake is sufficiently low, the tissues become depleted of their vitamin content. The loss occurs rapidly during the first week of thiamine deprivation, and subsequently more slowly. Even an animal showing severe deficiency symptoms retains approximately 20 per cent of its tissue thiamine. There is evidence that the brain releases stored thiamine more slowly than do other tissues. The tissue content of thiamine is increased if the intake is high.

Thiamine undergoes destruction in the body and is also excreted in the urine to the extent of approximately five to 10 per cent of the daily intake. The amount excreted bears some relation to the dietary intake, being low in thiamine-deficient animals and high in those fed an excess. A portion of the thiamine in tissues is constantly being destroyed in the process of metabolism. This rate of destruction largely determines the daily thiamine requirements and increases in proportion to the amount of food metabolized. The vitamin requirements can thus be raised by increasing the metabolic rate, whether by exercise, administration of thyroid, or forced feeding.

Physiological Function. There is evidence that thiamine plays a fundamental rôle in the intermediary metabolism of carbohydrate. The many steps in the cellular utilization of carbohydrate are accomplished by enzymes. These enzymes for the most part are composed of a protein molecule plus a prosthetic group. The prosthetic group in such a case is called the coenzyme. Neither the protein molecule nor the prosthetic group is independently active, but the two must be in combination. There is some evidence that a single prosthetic group may function in more than one enzyme system, but for the most part the coenzyme exhibits a marked specificity of action.

Neuberg and Hildesheimer, in 1911, discovered in yeast cells an enzyme called carboxylase, which functions in the conversion of pyruvic acid to acetaldehyde, as follows:

$$CH_3COCOOH + \text{Carboxylase} \longrightarrow CH_3CHO + CO_2$$

As can be seen, this reaction does not require oxygen and therefore is anaerobic. For a time it was thought that carboxylase required no coenzyme, and it was not until 1932 that Auhagen demonstrated that a substance called cocarboxylase was an essential constituent of the carboxylase system. Lohmann and Schuster (1937) obtained a highly purified concentrate of cocarboxylase and demonstrated it to be a pyrophosphate of thiamine. In other words, thiamine pyrophosphate is the prosthetic group of the enzyme carboxylase.

In the meantime, evidence accumulated that thiamine was also an essential for the intermediary metabolism of carbohydrate in animal tissue. Peters and associates (*see* Peters, 1936, *et seq.*) established the fact that the tissues of thiamine-deficient animals, notably brain, did not utilize oxygen at the rate characteristic of tissues of adequately nourished animals. Oxygen uptake could be increased by the addition of thiamine. Furthermore, pyruvic acid was found in the blood of experimental animals subsisting on a thiamine deficient diet. The amount of thiamine required to increase the oxygen uptake of thiamine-deficient tissue was of a magnitude which indicated that the vitamin must function in an enzyme system and that it was not in itself being oxidized. Therefore, there is strong evidence that thiamine constitutes the prosthetic group of an enzyme which assists in the oxidation of pyruvic acid in animal cells. This is an aerobic oxidation and therefore the particular protein component must differ from the carboxylase of yeast.

It is obvious that any deficiency in the oxidation of carbohydrate, a substance utilized by all cells, will lead to a marked physiological derangement involving many tissues. A thiamine-deficient subject shows symptoms suggestive of such a basic derangement. It is of particular interest, however, that in thiamine deficiency the nervous system is markedly affected and this is especially significant when one considers that nervous tissue with a respiratory quotient of unity is totally and uniquely dependent upon oxidation of carbohydrate for its functional integrity.

Symptoms of Deficiency. Severe thiamine deficiency leads to the condition known as beriberi. Beriberi was recognized as a disease entity long before the concept of vitamins was established and was one of the first deficiency diseases to be recognized. Although beriberi can be easily diagnosed and treated specifically, it is still a major cause of death in China, Japan, Brazil and certain other countries. The not infrequent occurrence of beriberi in its milder forms in the United States is only now being appreciated.

The chief symptoms of thiamine deficiency are related to the nervous and cardiovascular systems. The neurological symptoms and signs are characteristic of those attending peripheral neuritis. They begin with a sense of heaviness and weakness in the limbs. This is followed by marked sensory disturbances in the extremities such as localized areas of anesthesia or hyperesthesia, aching and burning. The nerve trunks are tender to pressure. There is a gradual loss of muscle strength and in extreme cases this may manifest itself in the form of foot or wrist drop, a shuffling gait, or even complete paralysis of a limb. The legs are usually affected to a greater extent than the arms.

The cardiovascular symptoms are equally prominent. It is often said that these develop late in the course of the deficiency but careful observations indicate that severe circulatory disturbances may be evident before the nervous system lesions have become sufficiently advanced to cause incapacitation. Weiss and Wilkins (1937) have made a detailed study of cardiovascular disease associated with nutritional deficiency. In thiamine deficiency the following symptoms and signs are characteristic: dyspnea on exertion with tachycardia and embryocardia, palpitation with gallop rhythm, prominent cardiac and epigastric pulsations, bounding peripheral pulse, enlarged heart, elevated venous pressure, edema, diminished vital capacity and abnormal electrocardiograms characterized chiefly by reversal of T waves, tachycardia and a prolongation of the Q–T interval. An interesting finding of considerable diagnostic importance is an increased velocity of blood flow due to arteriolar dilatation associated with the above signs of cardiac insufficiency (Figure 120).

Symptoms referable to the gastro-intestinal tract are also observed in severe cases of deficiency. Loss of appetite occurs early, and is followed by intestinal atony, constipation, and later by epigastric distress and tenderness. There is a form of thiamine deficiency known as *wet beriberi* which is characterized by extensive edema. The fluid is lost from the circulation largely as a result of hypoproteinemia from an inadequate intake of protein plus the added factor of poor cardiac function.

The severer grades of the deficiency disease in infants may run a rapid and fulminating course. Gastro-intestinal symptoms may herald the onset. They consist of loss of appetite, vomiting and greenish stools. This is soon followed by paroxysmal attacks of muscular rigidity during which the body is held tense and straight. The pulse becomes small and rapid, the face cyanotic, and the neck veins engorged. Dysfunction of the vocal cords may result in a characteristic type of plaintive cry or even in aphonia. Death may follow the initial symptoms in as short a time as 12 to 24 hours unless vigorous treatment is instituted.

The symptoms of *mild thiamine deficiency* are not as characteristic as those of the severe form and the condition may easily escape diagnosis. It is only within recent years that the attention of the physician has been directed to the possibility that thiamine deficiency may be fairly prevalent. The work of Cowgill (1934) on the vitamin B requirement of man offers a quantitative approach to this problem. It is now becoming more and more appreciated that beriberi is merely the fulminating type of a not uncommon deficiency disease. It is not only in the Orient that economic stress sufficient to limit the thiamine content of the diet exists. The symptoms consist of loss of appetite, muscular weakness, pains and paresthesias in the extremities, a tendency to edema, decreased blood pressure and low body temperature. The diagnosis may be confirmed by a careful study of the dietary history. Thiamine deficiency, however, may occur in association with an apparently adequate diet, for the vitamin is not stored in the body to a great extent. Thus, an increase in metabolic rate or gastro-intestinal disturbance, such as diarrhea of fairly long duration, necessitates an increased thiamine intake. Mild deficiency is also observed in infancy and childhood. The symptoms are pallor, loss of weight, restlessness, slight stiffness of the neck and spasticity of the extremities.

Bio-assay and Unitage. Despite introduction of crystalline thiamine which has largely replaced concentrates of the vitamin in therapeutics, it is still necessary to have a method of bio-assay and a standard of unitage. This is because the main source of intake of thiamine is the food which must be assayed for its vitamin content. Thiamine concentrates also are still employed.

Unfortunately, there is no official method for the bio-assay of thiamine and many procedures have been used. No less than three types of assay utilize the pigeon as a test animal. These methods depend upon the ability of the vitamin-containing preparations either to prevent or to cure polyneuritis or to maintain body weight. Other methods utilize the rat as a test animal. The Chase-Sherman unit, which formerly was widely employed, was measured by determining the ability of a preparation to maintain the rate of growth of rats. The many other methods of assay have been summarized by Williams and Spies (1938).

Fortunately, crystalline thiamine may be used as a basis of comparison in all the aforementioned tests. The international unit of thiamine activity has been established as the activity of three micrograms (0.003 mgm) of crystalline thiamine and has been adopted by the Council on Pharmacy and Chemistry.

Human Requirements. The human requirements for thiamine were approximated by Cowgill (1934) before the chemical nature of the vitamin was known. Cowgill made a study of the vitamin requirement of animals and supplemented these data with calculations of the vitamin content of human diets known to be associated with endemic beriberi. He concluded that the thiamine requirement is a function of metabolic rate and for a normal adult approximates 280 units a day (a little less than one mgm of thiamine). It is probable that these figures will undergo revision when it becomes possible to make acceptable chemical determinations of the concentration of the vitamin in body fluids. On the basis of Cowgill's formula, Jolliffe and coworkers (1939) fed normal subjects a diet calculated to contain approximately 50 per cent of the thiamine requirement.

Within five days the following signs and symptoms were noted; fatigue, lassitude, anorexia, precordial pain, burning of the feet, dyspnea on exertion, muscle cramps, palpitation, cutaneous hyperesthesia and electrocardiographic changes. All signs and symptoms disappeared following the addition of thiamine to the deficient diet.

The thiamine requirements are raised if for any reason absorption is faulty or utilization is increased as a result of an elevated metabolic rate, pregnancy or lactation. It has been estimated that infants probably require 50 to 75 units daily.

Preparations. *Thiamine Hydrochloride,* U.S.P. (*Vitamin B_1 Hydrochloride*), is a water-soluble, white crystalline material. Thiamine is marketed in oral tablets (containing one and five mgm each), in solution in one cc ampules (10 mgm), and rubber-capped vials containing 10 cc of a one per cent solution. The N.N.R. accepts for inclusion concentrates containing a minimum vitamin potency of 25 international units of thiamine per gram.

Therapeutic Uses. Obviously, the primary indication for thiamine therapy is in thiamine deficiency states, the symptoms of which have been described. Although beriberi is seldom encountered in the United States, it is now appreciated that milder forms of deficiency are quite prevalent.

Alcoholic Neuritis. Jolliffe and coworkers (1936) contributed evidence which indicates that alcoholic neuritis is basically a nutritional deficiency due to an inadequate intake of thiamine. Two factors contribute to bring about an inadequate intake in the chronic alcoholic addict. Appetite is usually poor and this leads to a diminished food intake. In addition, a large portion of the caloric intake is in the form of alcohol itself. Using Cowgill's technic, Jolliffe and coworkers calculated the vitamin intake of individuals suffering from alcoholic neuritis and found it to be inadequate in every instance. Therapy with crystalline thiamine or with diets high in thiamine content always resulted in an amelioration of symptoms. Patients who received 10 mgm daily of crystalline thiamine intravenously showed dramatic improvement within two or three days. When therapy was given in the form of vitamin rich foods, the rate of improvement varied directly with the vitamin content of the diet.

Neuritis of Pregnancy. It has been stated that pregnancy increases the thiamine requirement. The neuritis of pregnancy takes the form of multiple peripheral nerve involvement and the signs and symptoms in well developed cases resemble those described for beriberi. Evidence that neuritis of pregnancy is due to a dietary deficiency is supplied by the fact that it occurs when the diet is poor or in those with hyperemesis gravidarum. Proof that the neuritis is due to a thiamine deficiency is found in the dramatic clinical improvement observed after thiamine therapy. The dose employed is from five to ten mgm daily, given intravenously if vomiting is severe.

Other types of neuritis, in which it is difficult to conceive of any relationship to thiamine deficiency, have been treated with thiamine, seemingly with success. They include such unrelated conditions as trigeminal neuralgia and forms of neuritis associated with anemia, infections and drugs. It is difficult to determine, on the basis of scattered case reports, whether thiamine is responsible for the improvement observed in these cases and if so, whether it is acting specifically. The present view is that a vitamin is of therapeutic value only when a deficiency of that particular vitamin exists in the body. It is of utmost importance, therefore, to know whether the miscellaneous conditions mentioned are the result of thiamine deficiency. If not, and if thiamine unequivocally causes clinical improvement, the drug is probably acting in a manner not yet understood. One might venture the prediction, however, that thiamine, in the course of further experience, will be found valuable only when a deficiency state is present.

Cardiovascular Disease. The symptoms of thiamine deficiency referable to the cardiovascular system have been described. According to Weiss and Wilkins (1937) the incidence of cardiac disease from dietary deficiency in the poorer classes is higher than that of congenital heart disease or bacterial endocarditis. The deficiency can affect an otherwise normal cardiovascular system. The symptoms are partly of nervous and partly of myocardial origin, for accompanying the cardiac insufficiency there may be increased vagal reflex irritability. The latter

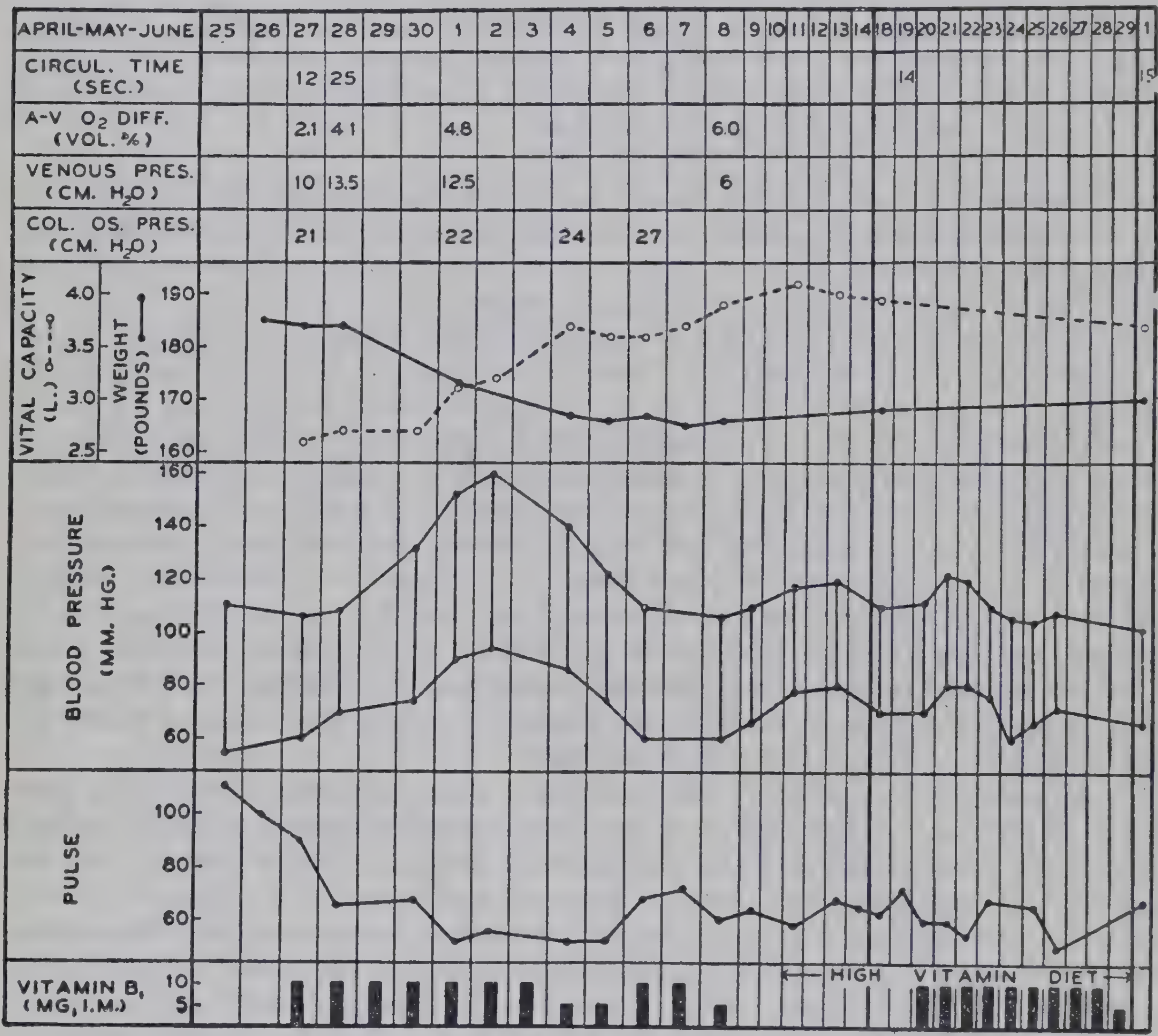


FIGURE 120. *The effect of thiamine on the clinical course of congestive heart failure of thiamine deficiency.*

Male, aged 36, chronic alcoholic addict with dietary history of a low vitamin intake, congestive failure of the circulation and polyneuritis. Thiamine was given in five mgm doses twice daily by intramuscular injection. Within 24 hours the rate of the heart slowed markedly, the speed of blood flow decreased toward normal and the arteriovenous oxygen difference increased. Within four days the vital capacity improved noticeably, the patient lost 12 pounds of edema fluid and marked clinical improvement was evident. Within 10 days the patient lost 20 pounds in weight and the vital capacity, the blood pressure (temporarily elevated by therapy), heart rate, venous pressure, serum colloidal osmotic pressure and femoral arteriovenous oxygen difference returned to normal. Note that once the status of the cardiovascular system had returned to normal, there was no further response to intensive thiamine therapy. The polyneuritis cleared and the patient was discharged at the end of the sixth week. (After Weiss and Wilkins, 1937. Courtesy of the *Annals of Internal Medicine.*)

disturbance manifests itself in the form of bradycardia with episodes of asystole and syncope. Cardiovascular disease of nutritional origin is most frequently observed in alcoholic addicts, pregnant women, persons with gastro-intestinal disorders, and those whose diet is deficient.

When the diagnosis of cardiovascular disease of dietary origin has been correctly made, the response to thiamine therapy is striking (Weiss and Wilkins, 1937; Dustin and coworkers, 1939) (Figure 120). As has already been stated, one of the pathognomonic features of the syndrome is an increased blood flow due to arteriolar dilatation. Within a few hours after the administration of thiamine, the rate of blood flow is reduced and the utilization of oxygen is increased as a result of the improved circulation. If edema is present due to myocardial insufficiency, diuresis results after proper therapy. The rate of improvement is seemingly proportional to the rate of onset and duration of the disease, and individuals suffering from a chronic deficiency may thus require protracted treatment. Weiss and Wilkins (1937) used as much as 100 mgm of thiamine daily in the treatment of their severe cases. This dose is probably excessive, but it is in no way harmful and may be employed to insure a surplus of vitamin.

Multiple Vitamin Deficiency. Many individuals ingesting an inadequate diet may suffer from a deficiency of more than one component of the vitamin B complex. Thus following the administration of nicotinic acid to a patient suffering from pellagra, secondary symptoms of beriberi may become prominent after the pellagra has been cured. Therefore, in the treatment of deficiency disease, it may be necessary to administer several components of the vitamin B complex. This can best be accomplished by adequate diet or by the use of preparations containing a number of dietary essentials, as for example, yeast. However, for diagnostic purposes or for rapid relief, the administration of thiamine alone is often indicated. The problem of the treatment of multiple vitamin deficiency has been reviewed by Spies and associates (1939).

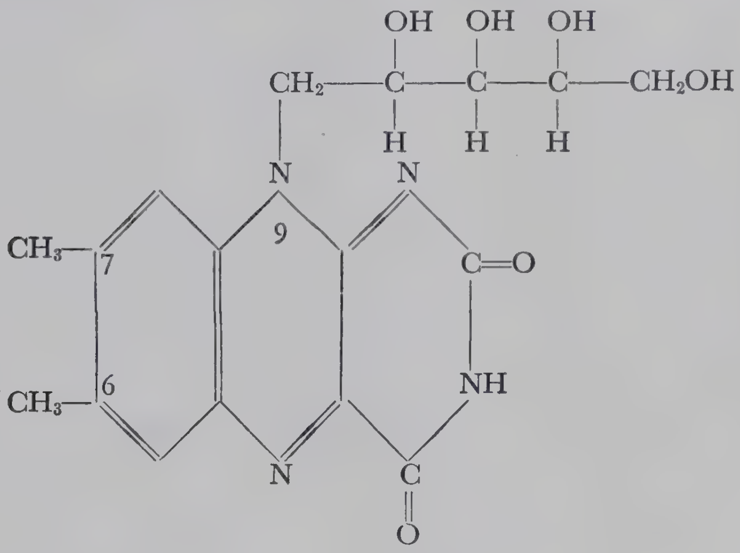
Gastro-intestinal Disorders. In experimental and clinical beriberi, certain symptoms are referable to the gastro-intestinal tract. On this meager basis, thiamine has been used uncritically as a therapeutic agent for such unrelated conditions as ulcerative colitis, gastro-intestinal hypotonia, chronic diarrhea, etc. At present, data for the evaluation of thiamine in gastro-intestinal disorders are insufficient. Unless the disease being treated is the direct result of a deficiency there is little reason to expect thiamine to act beneficially. Thiamine may be used, however, as a dietary supplement if it is believed that insufficient amounts are being absorbed. For example, in cases of chronic diarrhea, especially in infants, the prophylactic administration of thiamine may prevent the development of deficiency symptoms. The same principle probably holds true for patients with intestinal resections, fistulas, etc.

Other Uses. Favorable reports of thiamine therapy in numerous other disease syndromes have appeared. It is unfortunate that as soon as a vitamin is available in pure form, its indiscriminate use leads to an avalanche of uncritical clinical case reports concerning its use in a variety of unrelated diseases. An understanding of the basic physiology of the vitamins, however, readily allows one properly to select those clinical conditions in which there is an adequate rationale for specific vitamin therapy.

RIBOFLAVIN

Riboflavin was first identified in milk by Blyth (1879). At that time the substance was called lactochrome and its physiological significance was not appreciated. At a later date, the compound was obtained from other sources and was designated as lactoflavin because it had an intense yellow color. That lactoflavin was a component of the vitamin B complex was not appreciated until it was observed that concentrates of the so-called vitamin B_2 (G) had an intense yellow color, the intensity of which was related to the vitamin potency. It was soon demonstrated that crystalline lactoflavin had the same chemical properties and biological activity as the vitamin concentrates. All doubt as to the identity of vitamin B_2 and lactoflavin was removed when the latter was synthesized and the synthetic product was shown to be highly active. Lactoflavin is now commonly known as riboflavin, for it can be chemically distinguished from other flavins in that it contains a molecule of d-ribose attached to the chromophoric nucleus characteristic of the flavins.

Chemistry. Riboflavin has the following structural formula:



Riboflavin

Substances chemically related to riboflavin also possess physiological activity but one cannot deviate very much from the above structure without inactivating the compound. Thus, of all the side-chains that have been attached to the nitrogen in the 9 position, only the ribose- and arabinose-containing molecules exhibit vitamin activity. It is also essential to have a methyl group on either the 6 or 7 carbon atom. In the absence of such a methyl group, the compound possesses toxic properties.

Physiological Function. Riboflavin is apparently an essential constituent of the yellow oxidation enzyme. This enzyme is believed to be a phosphoric acid ester of riboflavin in combination with protein. It functions in cell respiration and is probably a constituent of all cells.

Symptoms of Deficiency. These have been observed mainly in experimental animals, notably the rat, but also in human beings. Animals deprived of riboflavin fail to grow, lose their hair, suffer from a nonspecific dermatitis, develop cataracts and exhibit premature aging. Riboflavin deficiency in human beings was first reported by Sebrell and Butler (1938) who fed an experimental diet to 18 women, in 10 of whom cheilosis developed after from 94 to 130 days. The lesions began as a pallor of the mucosa of the lip in the angle of the mouth without involvement of the buccal mucosa. Maceration and superficial fissures in the angles of the mouth and seborrheic accumulations at the nasolabial folds soon appeared. The lesions responded within five to 47 days when 0.025 mgm of riboflavin per kg of body weight was administered daily while the deficient diet was continued. Shortly thereafter spontaneous riboflavin deficiency in human beings was reported by Oden, Oden and Sebrell (1939) and Sydenstricker and associates (1939). In the following year another feature was added to the syndrome of riboflavin deficiency in man when it was appreciated that riboflavin deficiency may cause ocular manifestations (Kruse and coworkers, 1940; Sydenstricker and associates, 1940). These include photophobia, dimness of vision and actual impairment of visual acuity, congestion of the sclera, vascularization and opacities of the cornea, abnormal pigmentation of the iris, and interstitial keratitis. The lesions responded to the daily administration of five to 10 mgm of riboflavin. Kruse and coworkers suggested that the interstitial keratitis which frequently occurs in syphilis may actually be due to a riboflavin deficiency inasmuch as two of their patients suffering from keratitis associated with syphilis responded to riboflavin therapy.

Distribution and Excretion. Riboflavin is distributed throughout all body tissues. There is little storage of the vitamin and the feeding of large amounts leads only to increased excretion. Riboflavin is destroyed in the body at a slow rate and the dietary intake need only be equal to the rate of destruction for an optimal tissue concentration to be maintained. Emmerie (1936, 1937) followed the dietary intake and excretion of riboflavin in man, and found a daily excretion of 819 to 1250 micrograms. Restricting the intake reduces this figure whereas increasing the consumption of riboflavin leads to a more generous excretion. Ferrebee (1940) has also observed a relationship between the dietary intake and urinary excretion of riboflavin and describes methods for the estimation of the vitamin in urine. In lactating animals, a significantly large amount of riboflavin (20 per cent of the dietary intake) appears in the milk.

Human Requirements. The requirement of riboflavin for both children and adults approximates 100 micrograms (0.1 mgm) per 100 calories of food. All plant and animal cells contain the vitamin and in view of the wide distribution it is not surprising that clinical deficiency attributable to riboflavin is rare. However, it is the view of Sherman and Ellis (1934) that the optimal intake of riboflavin is probably much higher than the amount which is strictly necessary, and that the riboflavin content of foods should therefore be considered in the planning of the diet. The riboflavin content of various foods appears in the tables of Sherman and Lanford (1938).

Preparations and Therapeutic Uses. Riboflavin has been accepted for inclusion in N.N.R. The synthetic product is available in crystalline form and in ampules containing one mgm dissolved in two cc of a 10 per cent urea solution. It is stated in the N.N.R. that the compound is accepted for experimental purposes only, no therapeutic claims being advanced. The vitamin is probably valuable as an adjuvant in the treatment of multiple deficiency states such as pellagra (Spies and collaborators, 1939). The dose appears to be from two to three mgm, no side-effects being noticed from larger amounts. In frank riboflavin deficiency, doses of five to 50 mgm may be given orally or parenterally. The ocular manifestations of ariboflavinosis and their treatment with riboflavin have already been mentioned.

NICOTINIC ACID

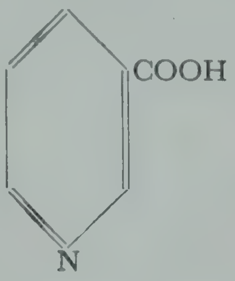
The classical work of Goldberger and his coworkers of the United States Public Health Service did much to establish pellagra as a deficiency disease resulting from an inadequate intake of what was then known as vitamin B_2 (G). Goldberger fed deficient diets to dogs and produced the condition known as "black tongue" which he believed to be analogous to human pellagra. Indeed, the same diet fed to man produced the classical signs and symptoms of pellagra. In rats, the diet caused a marked dermatitis. The three conditions could be cured by dietary measures. Many other theories of the etiology of pellagra were advanced by different workers, a prominent one being that the disease might arise from the ingestion of a toxin found in spoiled corn.

Long before Goldberger started his experimental study of pellagra, Funk (1913) isolated from rice polishings a compound which he identified as *nicotinic acid*. At that time the complex nature of vitamin B was not known. Funk determined that nicotinic acid was ineffective in the treatment of experimental polyneuritis and interest in the compound waned. Warburg and Christian in 1935 obtained nicotinic acid amide from a coenzyme isolated from the red blood corpuscles of the horse. In the same year, Euler, Albers and Schlenk (1935) obtained nicotinic acid from cozymase, and Kuhn and Vetter (1935) isolated the compound from heart muscle. These findings stimulated further studies on the nutritional value of nicotinic acid. Evidence was soon obtained that it was essential for the well-being of many species, but it was not at that time associated with any known dietary deficiency disease.

Meanwhile, riboflavin had been identified as vitamin B_2 (G) and interest centered around the value of this substance in curing black tongue in dogs, dermatitis in rats, and pellagra in man. It soon became evident that a lack of riboflavin was not the cause of this group of nutritional deficiency diseases and that there was another factor to be sought in the vitamin B complex. Liver extracts were known to be highly effective in curing human pellagra (Fouts and coworkers, 1936) and canine black tongue (Elvehjem and coworkers, 1937). Elvehjem and associates prepared liver concentrates highly effective in the treatment of canine black tongue, and soon (1937, 1938) identified the active substance as nicotinic acid amide. Proof was established by demonstrating that synthetic nicotinic acid derivatives were also effective in alleviating the symptoms of black tongue. Fouts and coworkers (1937) on this basis tested nicotinic acid for its ability to cure human pellagra and found it to be as effective as liver extract. Other clinical reports, notably the many contributions of Spies and coworkers (1938, *et seq.*), established the efficacy of nicotinic acid in the treatment of pellagra. The fact that this compound is effective in clearing the majority of symptoms of pellagrins who continue to ingest their deficient diet is strong evidence that nicotinic acid is a dietary essential, the lack of which is responsible for the disease.

Neither nicotinic acid nor riboflavin can cure the dermatitis of rats subsisting on a pellagra-producing diet. Although Goldberger was undoubtedly correct in ascribing to canine black tongue and human pellagra a common etiology, the dermatitis of rats is seemingly unrelated to either of these diseases. Rat dermatitis is relieved by what is apparently another factor of the vitamin B complex and this has been designated for the present as vitamin B_6.

Chemistry of Nicotinic Acid, and Relation of Structure to Action. Nicotinic acid is pyridine 3-carboxylic acid. As the name implies, it is related chemically to nicotine but possesses none of the latter's pharmacological properties. The structural formula of nicotinic acid is as follows:



Nicotinic Acid

Nicotinic acid, its amide and its sodium salt are equally effective in the treatment of pellagra. In addition to these compounds, many other related pyridine derivatives have been tested for their therapeutic efficacy in pellagra (Spies, Grant and Huff, 1938). The following compounds are effective, but probably less so than nicotinic acid: 2, 6-dimethylpyridine -3, 5 dicarboxylic acid; 3-5 pyridine dicarboxylic acid; 3-pyridine carboxylic acid diethylamide (coramine), and 3-methyl pyridine. Pyridine 2-carboxylic acid 2-methyl pyridine, and 3-amino pyridine are apparently much more toxic than nicotinic acid and of questionable benefit. The methyl betaine of nicotinic acid, although relatively non-toxic, is seemingly inactive.

Pharmacological Actions. Pyridine derivatives as a group possess rather marked pharmacological activity and it is therefore not surprising to find that nicotinic acid is not as inert in the body from a pharmacodynamic point of view as are other essential accessory food substances. The toxic dose for animals after intravenous administration is approximately four grams per kg (Chen and coworkers, 1938), and death occurs in convulsions. Oral administration of large amounts to dogs results in some cumulative action. For example, animals receiving two grams per kg daily show evidence during the second week of drug administration of marked intestinal irritation and also have convulsive seizures. One gram per kg, however, is well tolerated for a period of at least eight weeks. This is approximately 100 times the full therapeutic dose for man. Unna (1939), however, did not observe any cumulative action in rats, chickens or dogs.

Nicotinic acid is several hundred times less toxic than nicotine and does not possess the latter's actions on the autonomic nervous system (Hunt and Renshaw, 1929). It is also less toxic than nicotinamide (Unna, 1939). In human beings, nicotinic acid in therapeutic doses causes a transient vasodilatation which disappears within two hours and which is especially noticeable over the blush area. The flushing may be accompanied by itching and burning. Peripheral blood flow is increased (Abramson and coworkers, 1940) and the cutaneous temperature rises (Bean and Spies, 1940). This action is not shared by nicotinic acid amide.

Absorption, Fate and Excretion. Nicotinic acid is readily absorbed from the gastro-intestinal tract and all parenteral sites of injection. In the dog, it is excreted in the urine partially unchanged, partially conjugated with glycine and partially as the methyl betaine of nicotinic acid. The last-named product is therapeutically inactive even in high dosage. There have been few studies of the excretion of nicotinic acid in human beings. Vilter, Spies and Mathews (1938) devised a method for its chemical detection in urine and found nicotinic acid (or related compounds which may be detected by the method) to be absent from the urine of pellagrins but present in the urine of control subjects. Nicotinic acid appears in the urine of pellagrins after the administration of therapeutic doses. Euler and Schlenk (1939) found the concentration of nicotinamide in human blood to be 1.5γ per cc. Human beings excrete from five to 25 mgm per day of nicotinamide plus nicotinic acid.

Physiological Function. Nicotinic acid, in the form of its amide, is an integral portion of the molecule of certain cellular coenzymes which function in the promotion of cellular oxidations. Presumably this represents the physiological function of the vitamin and the reason why it is essential in human nutrition. The coenzymes containing nicotinic acid are diphosphopyridine nucleotide (cozymase, codehydrase, coenzyme I) and triphosphopyridine nucleotide (Warburg's coferment, codehydrase 2, coenzyme II). Diphosphopyridine nucleotide consists of a combination of one nicotinic acid group with one adenine, two pentose, and two phosphoric acid groups. It functions in a series of reactions in which hexose diphosphate is the substrate. Triphosphopyridine nucleotide contains one more phosphoric acid group and functions in a series of reactions in which hexose monophosphate is the substrate. Both coenzymes are widely distributed in all animal tissues. Experimental animals with a deficiency of nicotinic acid show a marked decrease in the cozymase content of the liver and muscles (Axelrod and Elvehjem, 1939). Also the blood level of diphosphopyridine nucleotide can be shown to vary with the intake of nicotinic acid, but the blood values are apparently of little value in the diagnosis of borderline cases of deficiency disease (Axelrod and coworkers, 1940). The details of the enzymatic reactions in which nicotinic acid amide is involved may be found in the reviews of Bauman and Stare (1939) and Barron (1939).

Symptoms of Severe Deficiency. The evidence is convincing that nicotinic acid is an essential dietary constituent, the lack of which leads to the clinical condition known as pellagra. It is not certain whether pellagra represents a single or multiple deficiency, but the onset of the important symptoms associated with the disease can be prevented by the addition of nicotinic acid to a pellagra-producing diet. Pellagra is characterized by signs and symptoms referable especially to the skin, gastro-intestinal tract and central nervous system. An erythematous cutaneous eruption resembling sunburn first appears on the back of the hands. Other areas exposed to light (forehead, neck and feet) are eventually involved, although the lesions may be more widespread. The cutaneous manifestations, which are characteristically symmetrical, may darken, desquamate and scar.

The chief symptoms referable to the digestive tract are stomatitis, enteritis and diarrhea. The tongue becomes very red and swollen and may ulcerate. There is also excessive salivary secretion and the salivary glands may be enlarged. Diarrhea is recurrent. The stools are watery, and may occasionally be bloody. Nausea and vomiting are also common. Gastric achylia is observed in about 50 per cent of the cases.

Symptoms referable to the nervous system consist of headache, dizziness, insomnia, depression and impairment of memory. In severe cases, delusions, hallucinations and dementia may appear. Motor and sensory disturbances of the peripheral nerves also occur.

In addition, certain cases of pellagra manifest a macrocytic, hyperchromic anemia (page 1137).

Symptoms of Mild Deficiency. A milder degree of deficiency has been termed "sub-clinical pellagra." The patients are nervous, irritable and complain of headache and insomnia. They also suffer from indigestion, occasionally nausea and vomiting, and may have diarrhea or constipation. A certain degree of pigmentation of the skin often exists and there is a burning sensation in the affected cutaneous areas.

Preparations. The preparations chiefly used in therapeutics are *Nicotinic Acid,* U.S.P., *Nicotinic Acid Amide,* N.N.R., and *Sodium Nicotinate.* These compounds exist as white, odorless crystals with a slightly bitter taste. Nicotinic acid is available in solution in vials containing 30 mgm in five cc or 10 mgm in 10 cc, and in tablets containing 25, 50 or 100 mgm each.

Therapeutic Uses. *Pellagra.* The specific use of nicotinic acid and its derivatives is in the prophylaxis and treatment of pellagra. In the acute exacerbations of the disease, therapy must be intensive. Spies and coworkers (1938) recommend the administration of the drug by the oral route in multiple doses. They have found 50 mgm given ten times daily to be effective in most cases. If oral medication is impossible, intravenous injection of 20 mgm in two cc of physiological sodium chloride solution is given two or more times daily.

The response to nicotinic acid is dramatic. Within 24 hours, the fiery redness and swelling of the tongue disappear and sialorrhea diminishes. Associated oral infections heal rapidly. Other infections of mucous membranes which are frequently seen, notably those involving the pharynx, urethra, vagina, and rectum, also disappear. Nausea, vomiting and diarrhea stop within 24 hours, and at the same time the patient is relieved of epigastric distress, abdominal pain and distention. Appetite also improves. Mental symptoms are quickly relieved, sometimes overnight. Confused patients become mentally clear and those who were delirious become calm, adjusted to their environment and remember with insight the events of their psychotic state. So specific is nicotinic acid in this regard, that it can be used as a diagnostic agent in patients with frank psychoses but questionable additional evidence of pellagra. The dermal lesions blanch and heal, but this response occurs more slowly. Nicotinic acid has less effect on cutaneous lesions which are moist, ulcerated or pigmented. The porphyrinuria, associated with pellagra, also disappears with nicotinic acid therapy.

Many cases of pellagra are complicated by thiamine deficiency and there is associated peripheral neuritis. This condition does not respond to nicotinic acid and must be treated with thiamine or a suitable vitamin B_1 concentrate. Many pellagrins are also benefited by additional therapy with riboflavin, and perhaps vitamin B_6 may prove to be a useful adjuvant.

Prophylactic Treatment. Spies, Grant, Stone and McLester (1938) made an extensive study of the value of nicotinic acid in the prophylactic treatment of pellagra. They selected a large group of patients with subclinical symptoms who could reasonably be expected to exhibit acute exacerbations of symptoms over the period of study. The experimental group received nicotinic acid daily, the control group no therapy. All the subjects were kept on their usual inadequate diet. All 22 control patients who were followed during the complete course of the experiment developed pellagra, whereas no symptoms of pellagra were evident in the 173 members of the experimental group protected by nicotinic acid. Furthermore, during the regimen of prophylactic therapy, there was definite amelioration of the symptoms of mild deficiency.

The *prophylactic dose* of nicotinic acid can be determined only by trial and error for there seems to be a wide variation in requirements. Thus Spies and coworkers found that some individuals remained in good health when receiving only 50 mgm a day in divided doses whereas others required 1000 mgm daily, a dose higher than that usually necessary in the treatment of acute exacerbations of the disease.

Side-Actions. Side-actions accompanying the use of nicotinic acid are few and mild. The first doses of the drug are likely to produce flushing, itching and burning of the skin and an increase of cutaneous temperature of one to two degrees C. The maximal effect occurs approximately 30 minutes after oral administration and ceases within a few hours. The reaction can often be circumvented by using smaller but more frequent doses or by the use of nicotinic acid amide. After large amounts of nicotinic acid, there is evidence of increased secretion of hydrochloric acid by the gastric glands, epigastric and abdominal cramps, increased peristalsis, belching, slight nausea and rarely vomiting. There is no consistent change in pulse rate, respiration, arterial blood pressure, oxygen consumption or the electrocardiogram. Sebrell and Butler (1938) have studied the vasomotor reactions of normal women receiving varying amounts of nicotinic acid daily. They observed flushing at unpredictable intervals, the frequency and intensity of which were apparently proportional to the dose.

Other Uses. There are as yet no proven indications for the use of nicotinic acid other than in the therapy and prophylaxis of pellagra. The drug has been tried for the treatment of psychoses unassociated with dietary deficiency and has been found to possess no therapeutic value. It has a unique value, however, as a diagnostic agent in the differentiation between psychoses of dietary and non-dietary origin (Cleckley, Sydenstricker and Geeslin, 1939). However, all cases of encephalopathy due to nicotinic acid deficiency do not necessarily occur in regions in which pellagra is endemic. For example, Jolliffe and coworkers (1940) have described an encephalopathic syndrome occurring in alcoholic addicts which is characterized by clouding of consciousness, cog-wheel rigidities and uncontrollable grasping and sucking reflexes. The syndrome is almost invariably fatal when treated by ordinary measures but the mortality was reduced to 13.6 per cent in a group of 22 patients treated with nicotinic acid in the dose of one gram daily by mouth plus 200 mgm daily of sodium nicotinate by intravenous and intramuscular injection. Although many of the patients failed to show any of the classical symptoms of pellagra aside from disturbances of the nervous system, Jolliffe and coworkers believe that the encephalopathic syndrome represents a complete deficiency of nicotinic acid. The dietary history of the patients and the specific effect of therapy with nicotinic acid support this view.

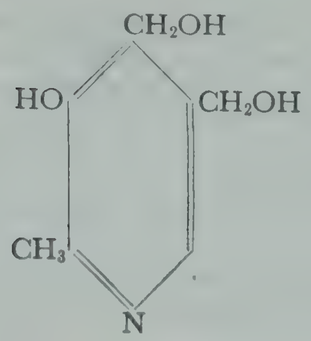
As is the case with other vitamins, nicotinic acid has been employed in the treatment of many conditions unassociated with vitamin deficiency but the clinical data are meager.

VITAMIN B_6

(PYRIDOXINE)

Vitamin B_6 is one of the components of the vitamin B complex known to be essential in animal nutrition. Although a discrete vitamin B_6 deficiency has not been described in man, evidence has been obtained from the treatment of multiple deficiency states that some of the symptoms accompanying the ingestion of inadequate diets may be the result of a B_6 deficiency.

The chemical nature of vitamin B_6 was established by Kuhn and associates (1939) and Stiller and coworkers (1939), and the vitamin was synthesized by Harris and Folkers (1939). It is a pyridine derivative with the following structural formula:



Vitamin B_6

The Council has assigned to vitamin B_6 and its hydrochloride salt the nonproprietary names *Pyridoxine* and *Pyridoxine Hydrochloride* respectively. No product has as yet been accepted for inclusion in N.N.R.

There is evidence that the physiological function of vitamin B_6 is linked with the utilization of unsaturated fatty acids (Birch, 1938). From a pharmacological point of view, pyridoxine is rather inert. The toxic dose in experimental animals after subcutaneous and oral administration is several grams per kg. Toxic symptoms are evident only after 24 to 48 hours and consist of convulsive seizures which may appear intermittently for several weeks. Small doses have no demonstrable actions on normal animals (Unna and Antopol, 1940). The intravenous toxic dose in rats and mice is over 0.5 gram per kg, the animals exhibiting convulsions before death. In man, intramuscular injections cause pain, but the oral or intravenous administration of 100 to 200 mgm is without untoward effect (Wiegand and coworkers, 1940).

Pyridoxine has not yet been employed extensively in therapeutics. It may be of definite value in the treatment of multiple vitamin deficiency. For example, Spies and coworkers (1939) observed that the administration of synthetic pyridoxine caused marked improvement in the residual neuromuscular symptoms of pellagra which were unrelieved by nicotinic acid, thiamine chloride and riboflavin. Antopol and Schotland (1940) reported that treatment with the vitamin resulted in considerable improvement in six cases of pseudohypertrophic muscular dystrophy.

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CHAPTER 71

WATER-SOLUBLE VITAMINS

II. ASCORBIC ACID (VITAMIN C)

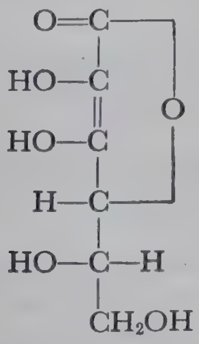
Scurvy was the first of the deficiency diseases to be recognized as such. As early as 1720, Kramer observed that medicines gave no relief in this condition, but ". . . if you can get green vegetables, if you can prepare a sufficient quantity of fresh antiscorbutic juices, if you have oranges, lemons, citrons, or their pulp and juice preserved with whey in cask, so that you can make a lemonade, or rather give to the quantity of 3 or 4 ounces of their juice in whey, you will, without other assistance, cure this dreadful evil."

Lind (1757), in his exhaustive treatise on scurvy, showed experimentally in human subjects that oranges and lemons incorporated in the diet could prevent the onset of the disease. In 1804 it became compulsory in England to issue a daily ration of lemon or lime juice to all British sailors. This led to the almost complete eradication of scurvy in the British navy and to this day the nickname "limies" is applied to British sailors.

Chemistry. The demonstration by Holst and Fröhlich (1907) that experimental scurvy could be produced in guinea pigs allowed for the bio-assay of the antiscorbutic vitamin and greatly aided investigations of the chemical composition of this substance. Nevertheless the combined efforts of many investigators during several decades were required to solve this problem. Zilva (1921) discovered that vitamin C could easily be destroyed by oxidation and could best be protected by reducing agents. He observed that concentrates with high vitamin content also contained powerful reducing substances but believed the latter merely accompanied the vitamin and protected it. McKinnis and King (1930) were of the opinion, however, that the vitamin itself was responsible for the reducing properties of the vitamin concentrates which they obtained from lemon juice.

Meanwhile, Szent-Györgyi had been studying the oxidizing mechanisms of the adrenal cortex and in 1928 he isolated from the adrenals a powerful reducing agent in crystalline form. He believed it to be a hexuronic acid derivative having the empirical formula $C_6H_8O_6$. Working on the assumption that this same compound might be concerned in the peroxidase system of plants, he succeeded in isolating it from cabbage and orange juice. Szent-Györgyi recognized this crystalline material as probably being identical with the reducing agent reported by Zilva to be present in vitamin C concentrates; but apparently he shared with Zilva the belief that the compound merely was a protector of the vitamin, for he failed, at that time, to test its antiscorbutic activity.

King and Waugh (1932) finally succeeded in isolating a crystalline compound from lemon juice concentrates, identified it as a hexuronic acid and demonstrated its potent antiscorbutic properties. A few weeks later, Svirbely and Szent-Györgyi announced that the hexuronic acid obtained from adrenal glands, cabbages and oranges also was highly antiscorbutic. Shortly thereafter, the exact chemical constitution of the antiscorbutic hexuronic acid was established independently by workers in several laboratories. It was soon synthesized and the synthetic product was shown to have the same biological activity as that isolated from natural sources. The structural formula of vitamin C is as follows:



Ascorbic Acid
(Vitamin C)

Ascorbic acid is an optically active compound. Only the levorotatory form possesses antiscorbutic activity. Compounds closely related chemically to l-ascorbic acid possess some antiscorbutic activity, but none compares in potency with the natural vitamin. The names ascorbic acid and cevitamic acid have been given to the vitamin. The former is more widely used and is the official terminology of the U.S.P.

Physiological Functions. The exact physiological function of vitamin C is unknown. The reducing properties of the vitamin foster the belief that ascorbic acid functions in cellular respiration and is essential in several oxidase enzyme systems. Although there is evidence of such a function in plants, conclusive proof that the vitamin is essential for oxidation in animal tissues is lacking.

From a study of the symptoms of vitamin C deficiency it becomes apparent that the vitamin is essential for the integrity of certain cells of mesenchymal origin. In the absence of ascorbic acid, the intercellular substance of mesenchymal cells is so changed that structural and functional deficiencies result. The collagen of all fibrous tissue, the matrices of bone, dentin and cartilage, and all non-epithelial cement substance including that of the vascular endothelium are affected.

Deficiency Symptoms. A deficiency in the intake of vitamin C leads to scurvy. The chief symptoms of scurvy arise from pathological lesions in the bones and blood vessels. In growing bones, lesions of the epidiaphysial junction lead to disunion, freedom of movement and traumatic fragmentation. In the rapidly growing bones of infants, a wide separation of the periosteum from the cortex occurs and massive subperiosteal hemorrhage may result. Subperiosteal hemorrhages also occur in adults. In the teeth, dentin is resorbed and atrophy and degeneration of odontoblasts occur in the pulp. The gums become spongy, bleed easily and may swell to such an extent that they overlap the teeth. Rarefaction of the alveolar bone results in the loosening of the teeth. Changes in the cells of capillary walls increase their fragility, and hemorrhage occurs in regions subjected to mechanical stress or trauma such as the skin, muscles, bones and gums.

Many of the contributions to the pathology of vitamin C deficiency have been made by Wolbach (*see* Wolbach, 1937; Dalldorf, 1938).

Pharmacological Actions. In the strict sense of the word, vitamin C may be said to possess few pharmacological actions. Administration of the compound in amounts greatly in excess of the physiological requirements leads to no demonstrable effects. In the scorbutic individual, however, administration of the vitamin leads to a rapid alleviation of symptoms. Purely secondary symptoms accompanying a deficiency disease are likely to be varied and associated with clinical scurvy there may be anemia, infections, metabolic disturbances, etc. As a result an extensive literature has accumulated concerning the effect of vitamin C on practically every function of the body. Contributions which may be of great importance have been lost under a deluge of clinical reports, many of which have little significance. The sifting of this information to extract the essential will probably require years.

Absorption, Distribution, Fate and Excretion. Vitamin C is the only vitamin for which accurate methods are available for quantitative determination. Consequently, much is known of the course of vitamin C in the body. Ascorbic acid is readily absorbed from the intestinal tract, absorption being almost complete after oral ingestion as evidenced by the absence of appreciable amounts of ascorbic acid in feces. However, under special circumstances, as for example in diarrhea, absorption may be limited. Also there is some indication that varying amounts of ascorbic acid may be destroyed in the gastro-intestinal tract, especially in individuals with achlorhydria.

After absorption, increased amounts of vitamin C can be detected in the blood. Ascorbic acid is normally present in both serum and cells. During active absorption, the concentration in serum is higher than in cells, but in the post-absorptive state the greater amount of the ascorbic acid in the circulation is intracellular (*see* Heinemann, 1938). Thus, analysis of whole blood probably gives a more accurate estimation of the ascorbic acid level than does analysis of serum. The absorbed ascorbic acid is ubiquitously distributed to all body tissues. The highest concentrations are found in glandular tissue, the lowest in muscle and stored fat.

The ascorbic acid content of the blood reflects the general state of saturation of the body as a whole and offers the best single index of the adequacy of the intake of ascorbic acid. An individual with a blood level of vitamin C of from 1.0 to 2.0 mgm per cent is completely saturated with the vitamin. Levels of approximately 0.5 mgm per cent may be designated as low normal. If the blood contains less ascorbic acid than 0.5 mgm per cent, the body concentration may be designated as suboptimal. Blood values below 0.15 mgm per cent are invariably associated with clinical scurvy.

Ascorbic acid is partially destroyed and partially excreted by the body. There is a renal threshold for vitamin C, however, and the vitamin is excreted by the kidney in large amounts only when the blood level exceeds this threshold, which is approximately 1.4 mgm per cent. The threshold may vary, however, in different individuals. When the body is saturated with ascorbic acid, the blood level will be approximately that of the renal threshold. If further amounts of the vitamin are then administered, most of it escapes into the urine. When the tissues are not saturated, however, and the blood level is low, the ingestion of ascorbic acid results in little or no renal excretion, for the tissue cells avidly take up the vitamin as it is absorbed and thus prevent the concentration in the blood from reaching threshold values. This forms the basis for the so-called "saturation test" for determining the requirements of vitamin C or the degree of saturation of a particular individual.

Human Requirements. Vitamin C is constantly being destroyed by the body, probably by oxidation. The daily intake of the vitamin must equal the amount oxidized if deficiency is to be avoided. Renal excretion influences the needs but little, for as has been explained, the vitamin is excreted in large amounts only when the body is completely saturated. The human requirement for vitamin C is known more accurately than for any other vitamin. It can be determined with exactness by means of the saturation test. In performing this test, an individual is first saturated with the vitamin and then placed on a diet free of vitamin C for a given number of days, after which the amount of vitamin required again to produce saturation is determined. This amount divided by the number of days on the vitamin-free diet represents the average daily amount of vitamin metabolized during the deficiency regimen. The index of saturation is the rapid urinary excretion of the major portion of the administered vitamin.

By the use of the aforementioned test, much has been learned of the metabolism of vitamin C. The saturated individual metabolizes more of the vitamin than one who is relatively deficient. As the amount of vitamin in the body decreases, the amount lost by destruction becomes proportionately less. For example, a saturated individual destroys approximately 0.8 mgm of ascorbic acid per kilogram of body weight per day. A person with a lower vitamin C reserve may destroy only half this amount. It is obvious, therefore, that a lower vitamin C intake is required to maintain adequate but suboptimal levels of vitamin C saturation than to maintain complete saturation.

In her comprehensive summary of the human daily requirements of vitamin C, S. L. Smith (1938) gives the following figures: infants, from about eight mgm (newly born) to 50 mgm; children, from 22 to 100 mgm or more; adults, from 28 to 100 mgm or more. These values represent roughly the range from the physiologically indispensable minimum to saturation or luxus consumption. Saturation rather than the physiological minimum is the desired goal for optimal nutrition.

Under certain circumstances, the rate of destruction and consequently the requirements for vitamin C are significantly increased. An outstanding example is the increased requirement of patients suffering from certain infectious diseases. An individual with tuberculosis may need 100 per cent more vitamin than a normal subject in order to remain saturated. Thus, tuberculosis may predispose to scurvy by increasing the requirements for vitamin C. Other conditions in which the vitamin C requirements are significantly raised are hyperthyroidism, peptic ulcer, neoplastic disease, pregnancy and lactation.

Preparations. *Ascorbic Acid,* U.S.P., B.P., consists of white or slightly yellow crystals or powder. The vitamin is marketed either as tablets or in powder form in sealed tubes. In addition, there are many foods which have a high vitamin C content. Orange and lemon juices are outstanding in this respect, containing approximately 0.5 mgm of ascorbic acid per cc. This high vitamin content permits the use of fruit juices in therapy in place of pure preparations of the vitamin. Indeed, in some localities, orange juice offers a much cheaper source of vitamin C than does crystalline ascorbic acid. Solutions of pure vitamin C are relatively unstable when exposed to air, whereas orange juice retains its activity for appreciable periods of time, especially if kept cold and protected from air.

Routes of Administration. Vitamin C is usually administered by the oral route, but in conditions which prevent adequate absorption from the gastrointestinal tract, it may be given by intramuscular or intravenous injection. For this purpose, ascorbic acid is dissolved in sterile water and the sodium salt is formed by the addition of an amount of sodium bicarbonate equal in weight to half that of the vitamin.

Therapeutic Uses. The specific therapeutic use for vitamin C is in the prophylaxis and treatment of scurvy. Whether vitamin C deficiency has a causal relationship to other clinical syndromes has not been established. In the prophylaxis of scurvy in infants and children, vitamin C is usually administered in the form of orange juice. The optimal intakes for varying age groups have been given above. An occasional infant is allergic to orange juice, and in such an instance ascorbic acid can be administered in solution. The ascorbic acid should be freshly dissolved.

In conditions in which the demands for ascorbic acid are increased, the vitamin C content of the diet should be fortified either with orange juice or crystalline ascorbic acid. The daily ingestion of 120 mgm of ascorbic acid is usually sufficient to meet the highest requirements.

In the treatment of fully developed scurvy, large doses of ascorbic acid may be given until the symptoms are under control. There is no evidence of toxic effects from large doses of ascorbic acid and one gram a day may be administered until the body stores have been replenished. Rarely a scorbutic individual may prove refractory to the oral administration of crystalline ascorbic acid and yet respond favorably to orange juice. The cause is unknown.

Vitamin C has been widely employed for the treatment of such conditions as dental caries, pyorrhea, gum infections, anemia, undernutrition, hemorrhagic states, miscellaneous infections, etc. While it is true that many of the above conditions may be associated with scurvy, their occurrence is not pathognomonic of scurvy. The final diagnosis of scurvy rests upon roentgenological evidence in the long bones and the chemical evidence of a low ascorbic acid content of the blood. Only then is there assurance that therapy with ascorbic acid will lead to beneficial effects. Despite the vast clinical literature on the various therapeutic indications for vitamin C (the conditions in which the vitamin has been reputed to give specific benefit run the gamut of most known diseases), there is no conclusive evidence that ascorbic acid is of value except in the relief of symptoms causally associated with scurvy.

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CHAPTER 72

FAT-SOLUBLE VITAMINS

I. VITAMIN A AND VITAMIN D

VITAMIN A

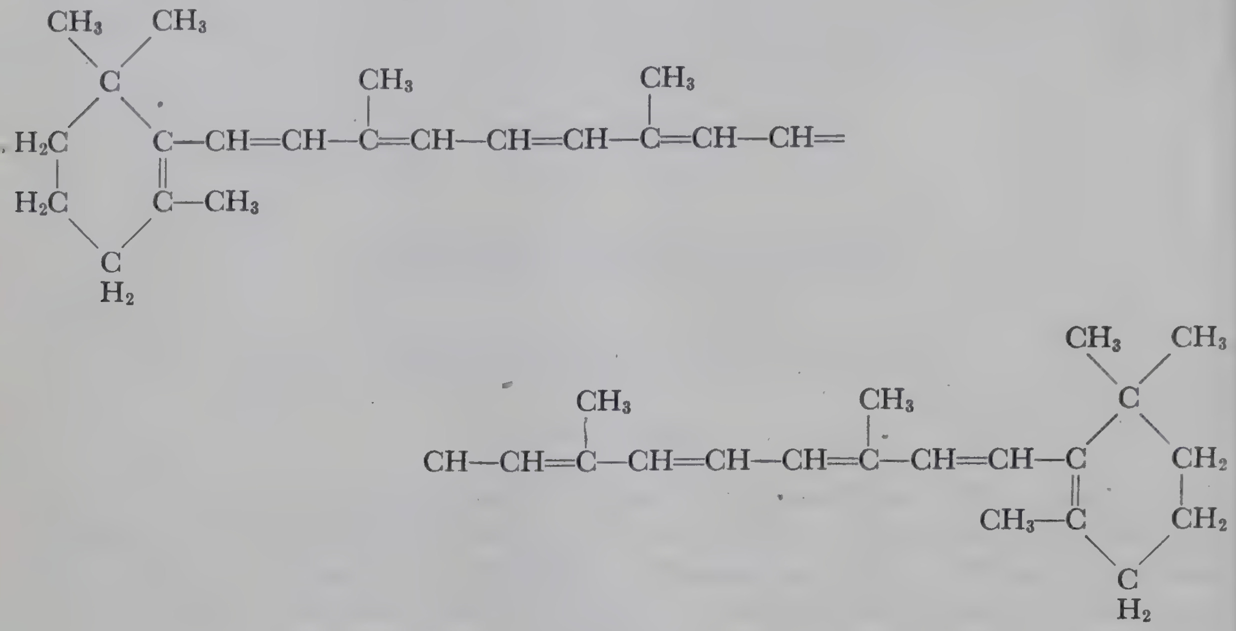
Certain of the symptoms of vitamin A deficiency were recognized in the middle of the nineteenth century, and their cause was linked to inadequacy of the diet. Thus the condition known as ophthalmia Brasiliana, a disease of the eyes which primarily afflicted poorly nourished slaves, was first described in 1865. In 1887, endemic night-blindness was reported to occur among the orthodox Russian Catholics who fasted during the Lenten period. More pertinent was the observation that the nurslings of mothers who fasted were prone to develop spontaneous sloughing of the cornea. Many other reports of nutritional keratomalacia soon followed from all portions of the world including the United States.

Experimental rather than clinical observations, however, led to the discovery of vitamin A. In 1913, Osborne and Mendel and McCollum and Davis simultaneously reported that animals fed on artificial diets with lard as a source of fat developed a nutritional deficiency which could be corrected by the addition to the diet of such substances as butter, milk-fat, egg yolk and cod liver oil. One of the outstanding symptoms of this experimental nutritional deficiency was xerophthalmia. Clinical and experimental vitamin A deficiencies were recognized as related during the World War of 1914–1918 when it became apparent that xerophthalmia in human beings was an aftermath of a decrease in the content of butter-fat in the diet.

Chemistry. The simple observation of Steenbock (1919) that, among the vegetable foods, the vitamin A content varied with the degree of pigmentation paved the way for the discovery of the chemical nature of the vitamin. Early experiments on the vitamin A activity of the plant pigment, carotene, failed to demonstrate that this substance possessed vitamin activity. However, it was soon appreciated that carotene was very sensitive to oxidation, and subsequently von Euler and associates (1929) and Moore (1929) demonstrated that purified carotene was a remarkably potent source of vitamin A. The daily protective dose of carotene for rats was found to be 0.003 mgm.

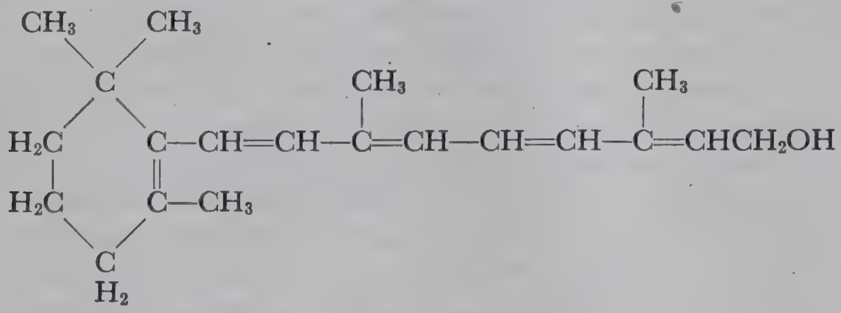
That carotene and vitamin A were not identical, however, was evident from certain differences in chemical and physical properties. Outstanding were the facts that vitamin A was not a pigmented substance and that the absorption spectra of the two materials differed. Also vitamin A was found only in the animal kingdom, whereas carotene prevailed in plants. It was then discovered that carotene is the precursor of vitamin A (provitamin A), and that it is broken down in the liver to the vitamin (Moore, 1930).

There are three types of carotene found in nature—alpha, beta and gamma. Beta carotene has the following structural formula which was established by Karrer and associates (1930):



β-carotene

In the body, beta carotene, which is a symmetrical hydrocarbon, breaks down to two molecules of vitamin A. The vitamin is a primary alcohol with the following structural formula, also established by Karrer and associates (1931):



Vitamin A

Alpha carotene and gamma carotene, although having the same molecular weight as beta carotene, are asymmetrical in structure and each gives rise to only one molecule of vitamin A. Therefore one milligram of beta carotene potentially has twice as much vitamin activity as one milligram of alpha or gamma carotene. Beta carotene predominates in nature. In addition to the carotenes, the plant pigment cryptoxanthin is converted in the animal body to vitamin A; but other plant pigments do not yield the vitamin.

Little can be done chemically to vitamin A before it loses its activity. The ring structure in vitamin A (β-ionone) is an integral portion of the molecule and only pigments containing this configuration can be converted into active compounds. Alpha and gamma carotene possess only one ionone ring whereas beta carotene has two. The activity of vitamin A is destroyed by hydrogenating or oxidizing the compound.

There is evidence that two forms of vitamin A may exist. These have been designated as vitamin A_1 and vitamin A_2. The former predominates in the tissues of salt-water fishes, the latter in fresh-water fishes. The livers of land animals contain vitamin A_1. The formula is that for vitamin A_1. The structure of A_2 that has been tentatively advanced differs only in that it contains one more vinylene group.

Physiological Function. Vitamin A has at least two important functions in the body. It plays an important rôle in vision in the retinal cycle and also is seemingly essential for the integrity of epithelial cells.

Vitamin A and the Retinal Cycle. It has long been known that a deficiency of vitamin A interferes with visual adaptation to dark, a condition known clinically as night-blindness or nyctalopia. The fundamental observations of Hecht (*see* review, 1937) and of Wald (1935, 1936, 1937) have contributed greatly to an understanding of this problem.

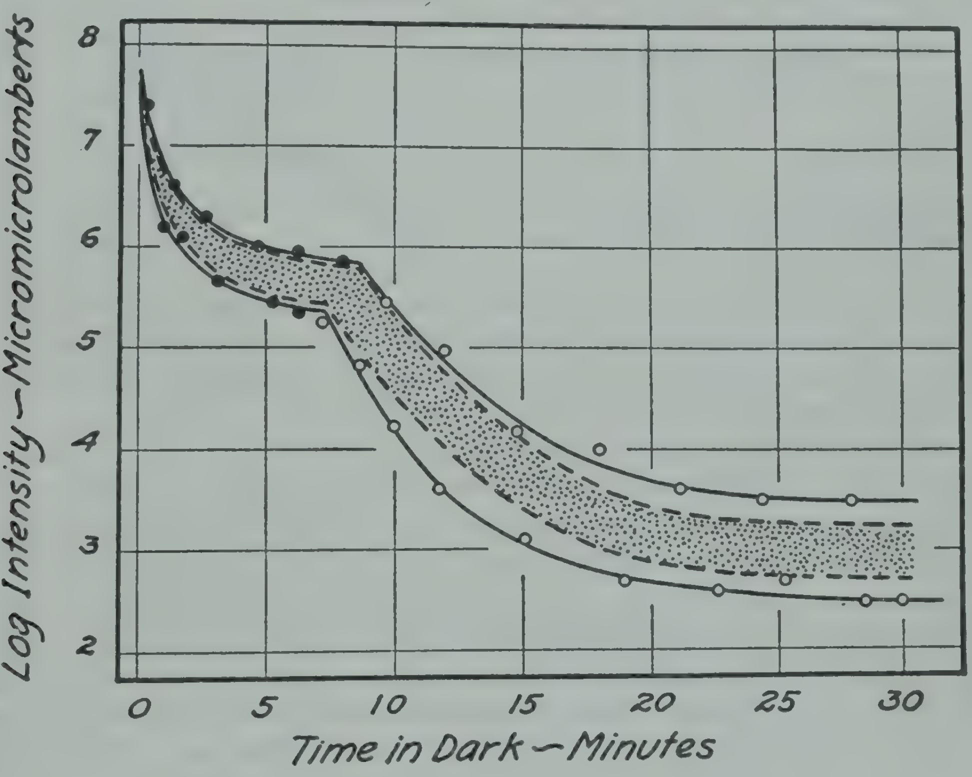


FIGURE 121. *The course of dark adaptation in 110 normal persons.*

Measurements were made by means of the Hecht-Shlaer adaptometer. The upper and lower curves represent the measurements obtained from the two subjects yielding the highest and lowest values of the final threshold. The results obtained from 80 per cent of the subjects fall within the dotted area. Primary cone adaptation is indicated by filled-in circles, secondary rod adaptation by open circles. The break in the slope of the curve represents the cone-rod transition time. (After Hecht and Mandelbaum, 1939. Courtesy of *The Journal of the American Medical Association.*)

Adaptation to dark is a function of both the rods and cones of the retina. Primary adaptation is accomplished rapidly by the cones and the process is completed in a few minutes. Secondary adaptation is a function of the rods, and this is not completed for thirty minutes or longer (Figure 121). The process of adaptation is a chemical one, and consists in the formation of photosensitive pigments in the retina which upon exposure to light of low intensity break down to initiate a nerve impulse. After break-down, the pigment is resynthesized. The photosensitive pigment of the rods is known as rhodopsin (visual purple). Rhodopsin is apparently a combination of a protein and prosthetic group, the latter being vitamin A, and is believed to be formed in the pigmented epithelium. Upon exposure to light, rhodopsin is converted to retinene (visual yellow) and this reaction initiates the nerve impulse. Retinene is partially reconverted to visual purple in a reaction which is the reversal of the photolytic breakdown of rhodopsin. A portion, however, goes to degradation products and must be re-synthesized to visual purple, a reaction which again involves vitamin A (Figure 122). A depletion of vitamin A retards the re-synthesis and reduces the available amount of rhodopsin. Consequently visual adaptation to dark is impeded. In all probability vitamin A is also concerned in an analogous manner in the formation of the photosensitive pigment of the cones, iodopsin.

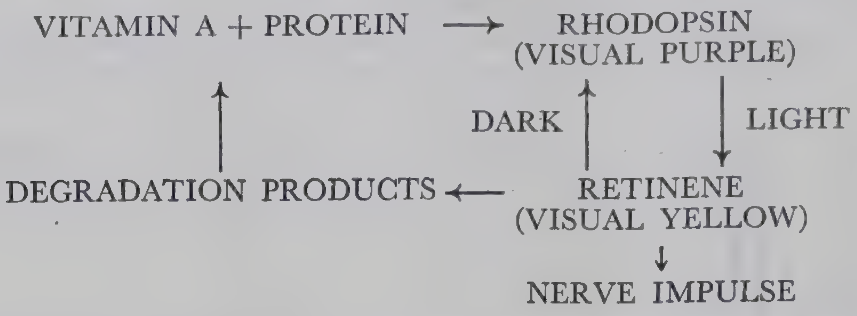


FIGURE 122. *Schematic representation of the chemical changes occurring in the visual cycle and the rôle of vitamin A.*

When human beings are fed diets deficient in vitamin A (Hecht and Mandelbaum, 1939), their ability for dark adaptation is soon affected. The threshold to light of both the rods and cones is progressively increased, the first change being detectable within a few days (Figure 123). Rod vision is affected more than cone vision. There is no change in the cone-rod transition time. Dark adaptation can be restored to normal by the addition of vitamin A to the diet. Some investigators are of the belief that the effect of vitamin A on nyctalopia of dietary origin can be detected within a few minutes, and vision becomes normal almost as rapidly as vitamin A gains access to the retina (Edmund and Clemmesen, 1936; Wald, Jeghers and Arminio, 1938). This would be expected if the deficiency were merely one of rhodopsin, the synthesis of which in the presence of an adequate supply of vitamin A occurs with the rapidity of a chemical reaction. It is difficult to see how the visual cycle could function at all unless the chemical synthesis of rhodopsin were rapid. However, Hecht and Mandelbaum (1939), in experiments on human subjects previously subsisting on a vitamin A deficient diet, report that normal vision is not restored until many weeks or even months after adequate amounts of the vitamin have been added to the diet. There is no adequate explanation for the wide discrepancy between these results and those of investigators who find a rapid correction of nyctalopia by vitamin A. It may be that the presence or absence of anatomical changes in the retina incident to the deficient diet is the factor conditioning the results obtained.

Vitamin A and Epithelial Structures. The function and structural integrity of epithelial cells throughout the body are seemingly dependent upon an adequate supply of vitamin A. The rôle of the vitamin in cellular function is unknown. Here again it may serve as the prosthetic group of an essential protein structure, but this is only conjectural. In the absence of vitamin A, epithelial atrophy occurs. This is followed by a reparative proliferation on the part of the basal cells. The new cells, by their continued growth, undermine and replace the original epithelium with a stratified, keratinizing epithelium. For the details of this process and the pathological lesions which are prone to follow, the reader is referred to the description of Bessey and Wolbach (1938).

Pharmacological Actions. Aside from its physiological functions, vitamin A appears to possess few other actions in the body. Isolated reports of toxic effects in animals from the administration of huge amounts of vitamin A have appeared, but carefully controlled observations indicate that the daily administration to rats, weighing 50 grams, of doses as high as 100,000 units has no deleterious effects (Vedder and Rosenberg, 1938). Apparently, vitamin A is one of the most innocuous of therapeutic agents. Individuals who ingest large amounts of carotene may exhibit carotenemia if the pigment is not readily converted to vitamin A by the liver. The skin temporarily becomes yellow, but the color soon fades and the condition is not harmful.

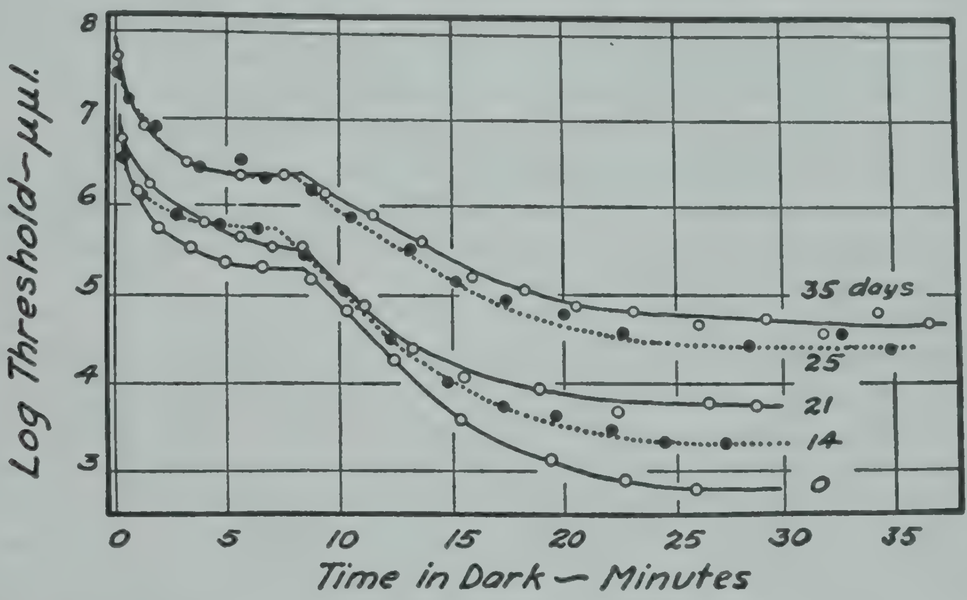


FIGURE 123. *Dark adaptation measurements obtained on a single subject at various times in the course of the dietary restriction of vitamin A.*

The diet is started at zero days and is continued for over a month. The filled-in and open circles merely keep the different sets of measurements apart and are smoothed by dotted and continuous lines, respectively. Note that rod vision is affected more than cone vision, as evidenced by the more rapid and extensive rise of the rod section of the curve during the diet, and that the cone-rod transition time is unaffected. Compare this figure with Figure 121. (After Hecht and Mandelbaum, 1939. Courtesy of *The Journal of the American Medical Association.*)

Severe Deficiency Symptoms. The symptoms of severe vitamin A deficiency are referable to the eye and epithelial structures in general. *Nyctalopia or night-blindness* is a constant finding. Individuals with nyctalopia adjust to dim light with great difficulty. When entering a dark motion picture house, for example, they may have to wait for as long as fifteen minutes before being able to find their way to a seat. When driving at night they become temporarily blinded after exposure to glaring headlights.

Another symptom of vitamin A deficiency related to the eye is *xerophthalmia.* This condition, which occurs very late in the course of the deficiency, is characterized by keratinization of the cells of the cornea. Ultimately ulceration of the cornea may result. Keratinization of epithelial cells also occurs throughout the body. Structural changes in the *broncho-respiratory tract* may lead to a high incidence of infections in the nose, accessory nasal sinuses, upper respiratory passages and lungs. Definite *cutaneous lesions* may be associated with a vitamin A deficiency. The skin as a whole becomes dry and keratinized. In addition there may be keratotic papular lesions especially on the arms and legs, although they may occur on any part of the body with the exception of the face. The lesion usually involves the pilosebaceous follicles. A high incidence of multiple *urinary calculi* accompanies vitamin A deficiency. The fact that the epithelium of the urinary tract shares in the general pathological changes of all the epithelial structures has led to the belief that epithelial débris provides the nuclei for the calculi which are formed. The possibility exists that dysfunction of the mucosa of the *intestinal tract* may be the cause of diarrhea which is sometimes associated with vitamin A deficiency. Defects or absence of *dental enamel and dentin* may result if a severe vitamin A deficiency is present during the period of tooth formation.

As is the case with all dietary essentials, a deficiency of vitamin A retards normal *growth and development*. The method of assay of vitamin A is based upon the ability of the vitamin to restore normal growth in rats fed a diet deficient in vitamin A but complete in all other respects.

Mild Deficiency Symptoms. The symptoms of a mild deficiency of vitamin A are merely the early manifestations of a severe deficiency. Here again, they are chiefly referable to the eye and to epithelial structures. Photophobia and poor adaptation to dark are the earliest signs. In addition to the changes in vision, the bulbar conjunctiva is dry and granular in appearance. Conjunctival smears show keratotic cells, and this may serve as an important diagnostic aid. Keratotic cells may also be observed in scrapings of the nasal mucosa and it is probable that all epithelial structures are undergoing beginning keratinization. The skin is likely to be dry and to show textural changes. A high incidence of infections involving epithelial structures is to be expected in individuals exhibiting these symptoms.

Daily Requirements. The human requirement for vitamin A can only be approximated from a limited number of studies which have attempted to correlate the symptoms of vitamin A deficiency with vitamin intake as determined by dietary history. The results of such experiments have been summarized by Booher (1938), who arrived at a figure of 1400 to 2000 units of vitamin A as the minimum intake of the normal adult for the prevention of night-blindness. It is probable that the optimal intake is higher than the figures quoted. For growing children and pregnant women, the requirement of vitamin A is probably even greater, and most authorities recommend a daily intake of 5000 to 6000 units.

Many studies have been conducted to determine the prevalence of vitamin A deficiency among representative groups of the population. In the majority of these undertakings, dark adaptation has been used as a measure of the degree of vitamin deficiency. Unfortunately widely divergent results have been obtained largely because of differences in technic of measuring dark adaptation. The problems involved have been reviewed by Hecht and Mandelbaum, (1939) and Isaacs, Jung and Ivy, (1938). Results of different groups of investigators vary so widely that it is not possible to state the incidence of mild degrees of vitamin A deficiency. As examples of contradictory reports may be cited those of Jeans and Zentmire (1936) and Jeghers (1937) on the one hand, as compared with the findings of Hecht and Mandelbaum and Isaacs, Jung and Ivy on the other, the former investigators claiming a much higher incidence than the latter.

Absorption, Fate and Excretion. Both vitamin A and carotene are readily absorbed when gastro-intestinal function is normal. If the amount of vitamin ingested is not much greater than the requirement, absorption is complete; but when huge excesses are taken, some of the vitamin may escape into the feces. Inasmuch as vitamin A and its precursors are fat-soluble, it is not surprising to find that their assimilation is closely related to the absorption of fat. Efficient absorption of vitamin A is dependent upon the presence of bile in the intestine, but even in the absence of bile some vitamin is utilized. The absorption of carotene, however, is almost completely inhibited by the absence of bile. Nor can carotene be absorbed in the absence of fat, whereas under this circumstance there is some assimilation of vitamin A. Conditions such as obstructive jaundice and steatorrhea reduce the absorption of the vitamin or provitamin so that deficiency can result in the presence of an intake which would otherwise be adequate. Large amounts of liquid petrolatum taken before meals can also reduce the absorption of carotene (Curtis and Kline, 1939). Certain infectious diseases appear to interfere with the absorption of the vitamin.

The maximum concentrations of vitamin A and carotene in the blood are observed five and eight hours respectively after their oral ingestion. These substances are removed from the blood stream by the liver, where they are deposited and stored, probably in the form of esters of fatty acids. There is evidence that both carotene and vitamin A are largely taken up by Kupffer's cells. These cells are also instrumental in the conversion of carotene to the vitamin, a reaction which is inhibited in certain diseases of the liver and in diabetes. For example, in juvenile diabetes the incidence of nyctalopia is high. The condition is readily corrected by vitamin A but not by carotene (Brazer and Curtis, 1940). Of the total vitamin A content of the body, 95 per cent is found in the liver. The amount of vitamin stored at this site depends upon the dietary intake. If intake is high, huge reserves are deposited in the hepatic cells. In fact, the feeding of excessive amounts of vitamin A to rats leads to the deposition of an amount of vitamin which at the normal rate of utilization would suffice the animal for many years. However, such excess stores are rapidly reduced when the diet becomes deficient. When depletion of the liver store is imminent, however, the vitamin is utilized more efficiently, and several months elapse before the symptoms of deficiency can be detected.

Steininger and coworkers (1939) have measured the carotene and vitamin A content of the blood of human subjects under controlled dietary conditions. They found that the blood concentration of these substances during fasting is related to dietary intake, being dependent partially upon the intake of the previous day and partially on the past diet. Inclusion of vitamin A in a deficient diet causes a rapid rise in blood values, but after withdrawal of the vitamin, the blood levels fall slowly, at varying rates in different subjects. Chemical measurement of vitamin A in the blood seems to be of some value in determining the nutritional status of a subject in that a consistently low fasting blood level probably indicates that the stores of vitamin A are being depleted whereas a high level is evidence of an adequate intake. No correlation was found between the amount of vitamin A in the blood and the ability to adapt to dark as measured by the biophotometer (*see* also Baum and McCoord, 1940).

Little vitamin A is eliminated in the usual channels of excretion, even when the intake is high, although it is probable that small amounts can be detected in all body fluids. Rather it is lost by destruction. However, one important avenue of elimination is the milk. The concentration of vitamin A in milk is proportional to the dietary intake only when the latter is low and the vitamin reserve of the liver is depleted. If the dietary intake of the vitamin is sufficiently adequate to permit storage in the liver, the concentration of vitamin A in the milk is maintained at a fixed maximum level. If intake is reduced, the liver stores are utilized before this characteristic level is altered. The vitamin A activity of milk is partially due to carotene and the ratio of vitamin to provitamin in the milk varies considerably in different species of animals.

Bio-assay and Unitage. Although vitamin A has been synthesized, the commercially available preparations are either vitamin concentrates from animal sources or mixtures of carotenes, the vitamin precursors. All preparations must therefore be bio-assayed for their vitamin activity. The present U.S.P. assay is based upon the ability of the vitamin to support growth in vitamin depleted rats of specified age and weight which are fed a standard diet deficient in vitamin A over a given period of time. One international unit of vitamin A is equivalent in activity to 0.6 microgram (0.0006 mgm) of crystalline beta carotene. The standard reference carotene is dissolved in coconut oil and protected from oxidation in solution by hydroquinone. The choice of the oily vehicle is important, for the availability of the carotene to the organism varies with the oil in which it is dissolved. The U.S.P. board of trustees supplies a reference cod liver oil, the vitamin A potency of which has been assayed against the international standard. One U.S.P. unit is the equivalent of one international unit.

Preparations. There are two types of commercially available vitamin A preparations, *fish liver oils,* and solutions of *carotene,* the vitamin precursor.

There are two official U.S.P. preparations of cod liver oil, *Cod Liver Oil,* U.S.P., a partially destearinated oil and *Non-destearinated Cod Liver Oil,* U.S.P. Both must contain a minimum of 850 units of vitamin A per gram. *Cod Liver Oil,* B.P., must contain a minimum of 600 units per gram. Cod liver oil consists of a thin oily liquid having a fishy odor and taste. Cod Liver Oil, U.S.P. may be flavored by the addition of not more than one per cent of official flavoring substances. Cod liver oil preparations included in the N.N.R. vary in potency from 850 to 2100 units per gram. Therefore it is necessary to know the strength of a particular preparation in order to determine the volume of the dose. The vitamin D content of cod liver oil is discussed on page 1284.

The chief advantage of cod liver oil as a source of vitamin A lies in its cost. It represents one of the cheapest forms of the vitamin available. The large amount which must be taken constitutes its main disadvantage. Many individuals object to the oily consistency and fishy taste of cod liver oil and the volume which must be administered is too large to be conveniently placed in capsules. The N.F. contains several emulsions of cod liver oil which are more palatable. Such preparations contain 30 to 50 per cent of cod liver oil. The U.S.P. also contains an *Emulsion of Cod Liver Oil* which contains 50 per cent cod liver oil and is flavored with syrup and oil of wintergreen.

Cod Liver Oil Concentrates, N.N.R. The disadvantages of cod liver oil can be circumvented by the use of cod liver oil concentrates. The concentrates are more expensive than cod liver oil because of the additional cost entailed in the chemical processing necessary in their production. Cod liver oil concentrates represent the unsaponifiable portion of cod liver oil dissolved in a suitable oily vehicle. To be acceptable for inclusion in N.N.R., a preparation of this kind must contain a minimum of 14,000 units of vitamin A per gram. Actually, some preparations contain as much as 60,000 units per gram. It should be kept in mind that in cod liver oil concentrates the content of vitamin D is increased in proportion to that of vitamin A. This type of preparation is chiefly of value when both vitamins A and D are required, as in infant feeding.

Halibut Liver Oil, N.N.R. This affords a vitamin preparation in which the content of vitamin A is very high in proportion to vitamin D. As much as one per cent of the weight of halibut livers may be vitamin A. For inclusion in N.N.R., halibut liver oil preparations must contain a minimum of 44,800 units of vitamin A per gram. Such preparations are of particular value when it is desired to give large amounts of vitamin A unaccompanied by large amounts of vitamin D.

Natural Vitamin A in Oil, U.S.P. This preparation was added to the U.S.P. XI (1939 Supplement) in order to allow fish liver oils other than cod liver to have an official status. Natural vitamin A in oil, in order to fulfill official requirements, must contain as fish liver oil alone, or as fish liver oil diluted with an edible vegetable oil, or as a solution of vitamin A concentrate of animal origin in fish liver oil or in an edible vegetable oil, between 50,000 and 65,000 units of vitamin A and not more than 1000 units of vitamin D per gram. Halibut liver oil is in this classification.

Percomorph Liver Oil, N.N.R. This is the richest source of vitamin A. In its marketed form, it is diluted 50 per cent with cod liver oil to yield a preparation which contains 60,000 units of vitamin A per gram. Percomorph liver oil also contains large amounts of vitamin D.

Natural Vitamins A and D in Oil, U.S.P. This is another preparation that was added to the U.S.P. XI (1939 Supplement) in order to allow fish liver oils other than cod liver oil to have an official status. Natural vitamins A and D in oil, in order to fulfill official requirements, must contain 50,000 to 65,000 units of vitamin A and 10,000 to 13,000 units of vitamin D per gram, either as fish liver oil alone, fish liver oil diluted with an edible oil, or solutions of vitamin A and D concentrates from animal sources in fish liver oil or in an edible vegetable oil. Percomorph liver oil is the natural product which can meet these specifications as can also cod liver oil concentrates.

Burbot Liver Oil, N.N.R. This contains a minimum of 4480 units of vitamin A per gram, and thus is approximately five times as active as cod liver oil in this regard. Burbot liver oil is also a good source of vitamin D and may be employed when the actions of both vitamins are desired.

Shark Liver Oil, N.N.R. Shark liver oil is extracted from the livers of various species of sharks. It contains not less than 16,500 units of vitamin A and not less than 40 units of vitamin D per gram. Like halibut liver oil, the preparation is chiefly of value when it is desired to administer large amounts of vitamin A unaccompanied by large amounts of vitamin D.

Carotene, N.N.R. This is the only preparation which supplies vitamin A without vitamin D. Carotene is available dissolved in cotton seed oil in the concentration of 7500 units per gram.

Therapeutic Uses. As has already been stated, the epithelial lesions which result from a vitamin A deficiency increase the vulnerability of the structures involved to infection. Consequently, vitamin A has been popularly termed the "anti-infective" vitamin. It is this term which is responsible for the wide misconception which exists regarding the value of vitamin A in preventing and combating infections. There is no doubt that an individual suffering from a vitamin A deficiency is prone to develop infections especially of the respiratory tract, and that this condition can be corrected by the inclusion of adequate amounts of vitamin A in the diet. A fact that bears emphasis, however, is that there is no evidence that an excessive intake of vitamin A will influence the incidence of infections in a group of individuals whose intake of vitamin A is already adequate. The experiments which support this statement are numerous. Many of them have been briefly reviewed by Clausen (1938), who concludes that no justification exists for calling vitamin A the "anti-infective vitamin" inasmuch as there are many other factors involved in infection which are of equal or greater importance.

The wide practice of prescribing vitamin A, especially during the winter months, for the prevention of colds and upper respiratory infections, is open to justified criticism if the physician administers the vitamin to a person whose diet is already adequate. The diet low in vitamin A should be corrected by foods rather than drugs. However, it should be stated that large amounts of vitamin A apparently can do no harm, and often a physician is almost forced to prescribe vitamins for the well-misinformed individual who reads and hears so much of the anti-infective vitamin A. If vitamin A is prescribed as a dietary supplement there is no reason to believe that 50,000 units daily is any more beneficial than 5000 units, the latter figure being well above the daily requirement.

Vitamin A has been prescribed in many other conditions for reasons which also do not bear scientific scrutiny. For example, cod liver oil has been used locally for the treatment of infections, burns and wounds. Carefully controlled observations fail to substantiate the claims advanced for such uses in early enthusiastic reports. Also large amounts of vitamin A have been employed for the treatment of many systemic disorders, but there is little or no clinical or experimental basis to support this practice.

The legitimate uses of vitamin A are in the treatment of vitamin A deficiency and in its prophylactic administration during periods of high requirement, such as infancy, pregnancy and lactation. Although no definite statement can be made as to the incidence of vitamin A deficiency, there is little doubt that limitation in diet due to economic stress or food fads can give rise to the symptoms of deficiency as outlined above. Once a vitamin A deficiency has been diagnosed, intensive therapy should be instituted. Thirty thousand to 50,000 units of vitamin A should be given daily until the desired clinical response is obtained. The patient may then be sustained by a proper diet.

Rarely, the absorption or storage of vitamin A may be adversely affected and under such circumstances long-continued therapy with the vitamin may be indicated. An individual with steatorrhea or high-grade biliary obstruction may require a larger intake of the vitamin than can be provided by the diet in order to avoid the symptoms of deficiency. Cirrhosis of the liver may so interfere with the storage of vitamin A or the conversion of carotene to the vitamin as to require the administration of dietary supplements (*see* Patek and Haig, 1939).

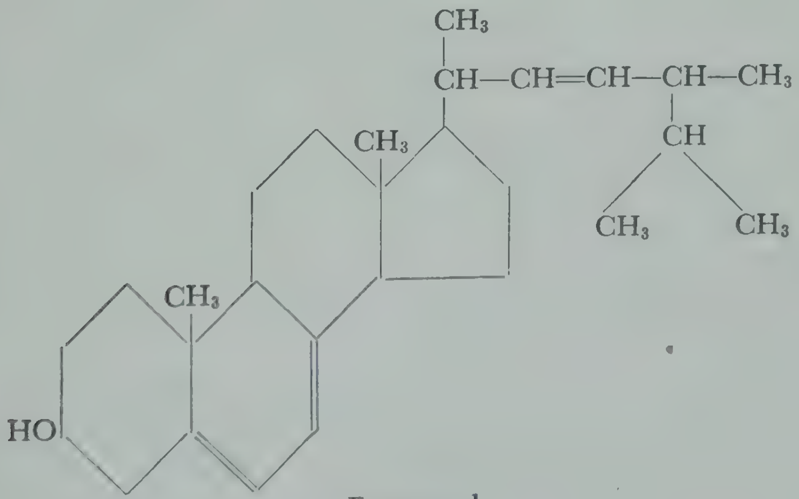
During infancy, pregnancy and lactation, it is best to supply supplemental vitamin A rather than rely solely upon the dietary intake. Infants usually receive vitamin A in conjunction with vitamin D, for these two substances occur together in fish liver oils. If however, a purified source of vitamin D is used, there is a real possibility, even though the diet of an infant is rather high in vitamin A, that the diet may not contain an amount which is optimal. In the opinion of some pediatricians, this constitutes a real objection to the use of solutions of crystalline vitamin D rather than a preparation of fish liver oil for the prophylaxis of rickets. A daily intake of 5000 units of vitamin A should be provided for infants and growing children. During pregnancy and lactation, the intake of vitamin A should also be maintained at 5000 units per day.

VITAMIN D

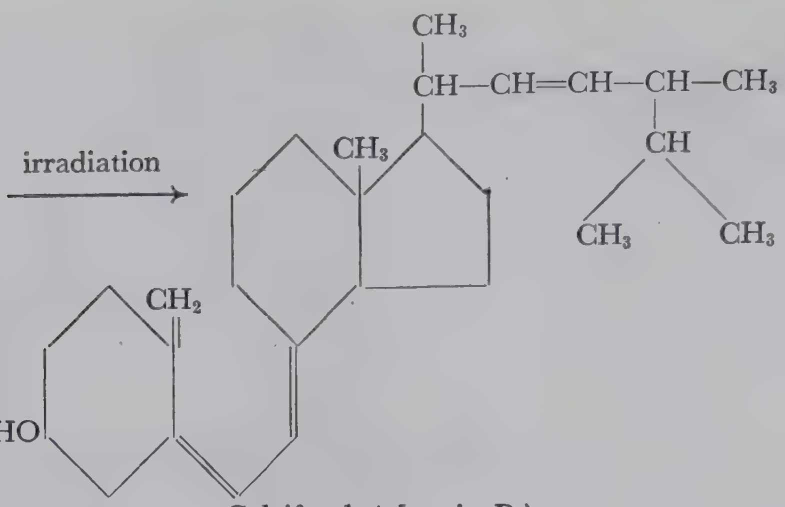
Before the discovery of vitamin D, approximately 80 per cent of urban children suffered from rickets. Two theories as to the etiology of this disease gained wide credence. One expressed the belief that rickets resulted from a deficient diet, whereas the other attributed the syndrome to a lack of fresh air and sunshine. The classical studies of Mellanby (1919), who showed that experimental rickets could be prevented by cod liver oil, and of Huldschinsky (1920), who demonstrated the efficacy of sunlight and ultraviolet light in the prevention of rickets, seemingly had no common denominator until it was demonstrated independently by Hess and Weinstock and by Steenbock and Black in 1924 that ultraviolet irradiation could impart antirachitic activity to foods. Subsequent investigations led to the chemical identification of vitamin D and its precursors and to some understanding of its basic mechanism of action.

Chemistry and Relation of Structure to Action. It was first believed that cholesterol was the substance in food which became antirachitic after ultraviolet irradiation. Further study showed the vitamin precursor to be ergosterol. For several years thereafter, it was assumed that vitamin D was a single chemical entity which resulted from the irradiation of ergosterol. It soon became evident, however, that the results obtained from the bio-assay of a series of vitamin D preparations in one species of experimental animals did not agree with those obtained by the use of a different test animal. This indicated that there were at least two active components in the materials assayed and that these components behaved differently in heterologous species. Chemical investigations have revealed that there are many different precursors which can be changed by irradiation into compounds having vitamin D activity. Also it has been established that the progressive irradiation of a single vitamin D precursor can result in the formation of a series of compounds, each member of which has a different degree and type of physiological activity.

There are at least ten different substances which possess vitamin D activity. All have the same general chemical structure, being derivatives of cyclopentenophenanthrene. It is of interest to recall that the sex hormones, the adrenal cortical hormone and the cardiac aglycones have this same basic structure. Of the many substances having vitamin D activity, two are of outstanding importance. They are the products of the irradiation of *ergosterol* and *7-dehydrocholesterol*. When ergosterol is exposed to ultraviolet radiation, one of the several successive products formed is known as *calciferol* or *vitamin D_2*. The effect of irradiation is to change the internal configuration of the ergosterol molecule. The following reaction takes place:

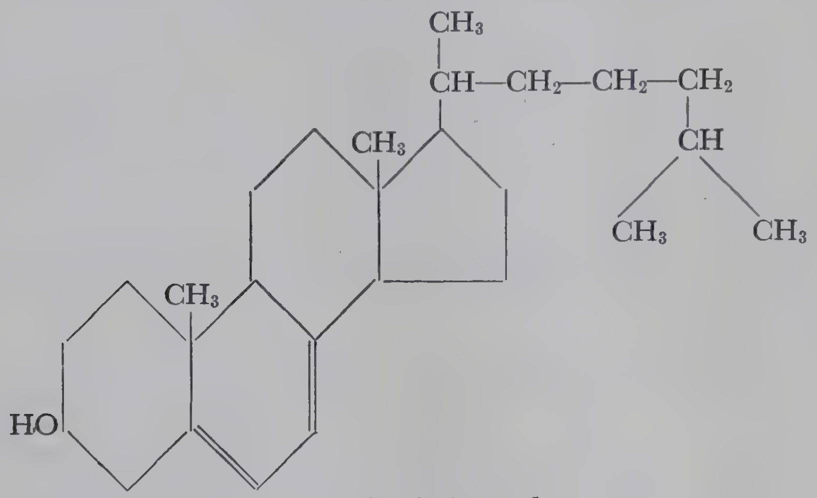


Ergosterol

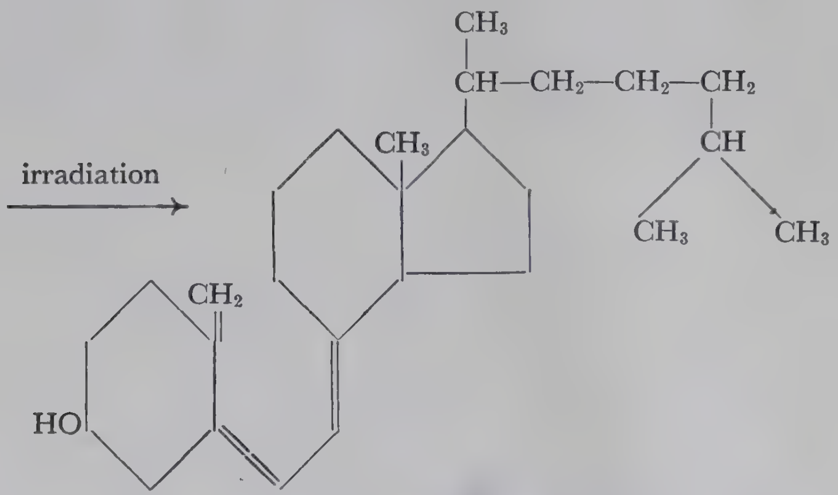

irradiation
CH₃
CH—CH=CH—CH—CH₃
CH
CH₃
CH₃
CH₃
CH₂
HO

Calciferol (vitamin D_2)

The irradiation of 7-dehydrocholesterol results in the formation of *vitamin* D_3 or *activated 7-dehydrocholesterol.* The reaction is as follows:


CH₃
CH—CH₂—CH₂—CH₂
CH
CH₃
CH₃
CH₃
CH₃
HO

7-dehydrocholesterol


irradiation
CH₃
CH—CH₂—CH₂—CH₂
CH
CH₃
CH₃
CH₃
CH₂
HO

Activated 7-dehydrocholesterol
(vitamin D_3)

The antirachitic potencies of the two activated sterols differ greatly from each other in certain species, but less so in man. Therefore, for therapeutic purposes, there is no practical difference between the two preparations. Vitamin D_3 is obtained from animal sources and is the form of the vitamin found in irradiated milk, and with numerous other antirachitic substances in fish liver oils. It is also formed in the skin when an individual is exposed to sunlight. Ergosterol, on the other hand, is found in plants, and activated ergosterol or calciferol is the active constituent in commercial vitamin preparations such as viosterol, irradiated yeast, irradiated bread, etc.

When ergosterol is irradiated, calciferol is only one of a series of products which are formed. Windaus and associates (1929) studied the photochemical reactions involved in the transformation of ergosterol which may be expressed as follows:

$$\begin{tikzcd}
 & & & & & \text{Suprasterol I} \\
\text{Ergosterol} \arrow[r] & \text{Lumisterol} \arrow[r] & \text{Tachysterol} \arrow[r] & \text{Calciferol} \arrow[r] & \text{Toxisterol} \arrow[ur] \arrow[dr] & \\
 & & & & & \text{Suprasterol II}
\end{tikzcd}$$

These compounds are closely related chemically, but show marked differences in their physiological properties, as will be described. In the following discussion, vitamin D will be used as a collective term for vitamins D_2 and D_3.

Physiological Functions and Pharmacological Actions. Vitamin D is intimately concerned with the metabolism of calcium and phosphorus, but the exact rôle which it plays has not been established. Deposition of calcium salts in growing bone depends upon the maintenance in the blood of normal concentrations of calcium and phosphorus. The factors influencing the amounts of calcium and phosphorus in the blood are the dietary intake and intestinal absorption of these elements, the activity of the parathyroid gland, vitamin D, and the acid-base balance of the blood. Evidence points to the fact that the main function of vitamin D is concerned with the intestinal absorption of calcium and phosphorus but the vitamin may also function in the conversion of organic to inorganic phosphate in bone (Cohn and Greenberg, 1939). In the absence of vitamin D, the amount of calcium and phosphorus absorbed through the intestine is diminished. In man, so essential is vitamin D that in its absence, even in the face of a plentiful dietary intake of calcium and phosphorus in a ratio best designed for bone formation, the condition known as *rickets* results. On the other hand, in the presence of an adequate dietary intake of vitamin D, the concentration of calcium and phosphorus in the circulation not only remains within normal limits, even when the ratio of these elements in the diet is markedly distorted, but rickets can be prevented or cured.

Rickets as it occurs clinically is associated with the excretion of large amounts of unabsorbed calcium and phosphorus in the feces. The blood level of phosphate is usually reduced; that of calcium, however, may approximate normal, for seemingly there is a hyperfunction of the parathyroid glands in rickets which tends to maintain the normal concentration of calcium. The calcium is withdrawn from the bones, however, and although the serum calcium level is preserved structural abnormalities of the bones develop. This point is emphasized in experimental studies which have demonstrated that rickets can be exaggerated by the administration of parathyroid extract whereas it is more difficult to produce the condition in the absence of the parathyroid glands.

In the animal organism, therefore, there are two primary factors in the control of calcium and phosphorus metabolism. Vitamin D is chiefly concerned with the intestinal absorption of calcium and phosphorus and in this manner helps maintain normal levels of these elements in the blood. The parathyroid gland, on the other hand, seemingly does not influence the absorption of calcium and phosphorus, but rather mobilizes these elements from the skeleton. The view has been presented that parathyroid substance exerts its primary action on phosphate metabolism by virtue of the marked phosphaturia which it causes. The phosphaturia, in turn, is probably the mechanism by which calcium is drawn out of the bones (page 1175).

There is some evidence that vitamin D may exhibit certain aspects of parathyroid activity. Albright and associates (1938) have studied the effect of the vitamin on calcium and phosphorus metabolism in parathyroprivic patients. They found that vitamin D promotes the renal excretion of phosphorus as well as the intestinal absorption of calcium and this former action is similar in character to that of parathyroid extract but less in degree (Figures 124 and 125).

Furthermore, Windaus and associates advanced the suggestion that the various irradiation products of ergosterol have an action other than antirachitic, for although the series as a whole markedly influences calcium metabolism its members are not equally antirachitic and some are many times more toxic than others.

Toxic Action of Compounds Possessing Vitamin D Activity. When huge amounts of vitamin D are given to animals (1000 times the antirachitic dose), the calcium and phosphate concentrations of the blood rise above normal. Furthermore, the calcium and phosphorus balance becomes negative, indicating the withdrawal of these elements from the skeleton. Metastatic calcification also takes place, chiefly in the renal tubules, the blood vessels, heart, bronchi and stomach. There is likewise evidence of degenerative changes in the liver. This type of toxic action is similar to that produced by parathyroid extract.

At one time it was believed that the toxic dose of vitamin D was not many times greater than the therapeutic dose. Many reports, especially in the German literature, appeared regarding this toxicity. In the light of our present knowledge it is probable that the toxic symptoms resulted from the improper irradiation of ergosterol, and the product obtained was low in vitamin D content and high in toxic irradiation products. Of the series of compounds produced by the irradiation of ergosterol, calciferol has the most marked antirachitic action and a comparatively low toxicity. On the other hand, toxisterol has little antirachitic action but is highly toxic by virtue of increasing the calcium level of the blood and causing metastatic calcification. A possible interpretation of this effect of toxisterol is that it produces a primary phosphaturia and in this way decalcifies bones and produces hypercalcemia.

Summary. The chief function of vitamin D is to promote the intestinal absorption of calcium and phosphorus and thus maintain a blood concentration of these elements optimal for calcification of bone. A secondary action may promote the renal excretion of phosphorus, which would result in mobilization of skeletal calcium. The effective antirachitic compounds are those which have their chief effect on calcium absorption.

Parathyroid extract mobilizes calcium from bone and has no effect on its intestinal absorption. This action may be secondary to a phosphaturia and favors the production of rickets and other bony abnormalities.

There is a group of compounds obtained from the irradiation of ergosterol and chemically related to vitamin D which appear to simulate the action of the parathyroid hormone more than that of the vitamin. These preparations are not antirachitic but rather have therapeutic usefulness in the treatment of hypoparathyroidism.

Deficiency Symptoms. The signs and symptoms of vitamin D deficiency are too well known to bear repetition. In infants and growing children, a deficiency of the vitamin results in rickets and impaired dentition. In the adult, a deficiency in the absorption of calcium and phosphorus, in which a lack of vitamin D can be one of the contributing causes, leads to adult rickets or osteomalacia.

Absorption, Fate and Excretion. Vitamin D is absorbed from all sites of administration. In a suitable fatty vehicle it can penetrate the intact skin. It also gains access to the circulation after subcutaneous or intramuscular injection. The most efficient route of administration is the gastro-intestinal tract. Greaves and Schmidt (1933) showed, in experiments on rats, that bile is essential for the optimal intestinal absorption of vitamin D and that desoxycholic acid is the most important constituent of the bile in this regard. The feces of animals receiving potent sources of vitamin D possess considerable antirachitic activity, and it has been estimated that approximately 25 per cent of the orally ingested vitamin ordinarily escapes absorption. There is evidence that when vitamin D is taken in a relatively dispersed medium as in cod liver oil, assimilation is greater than when it is ingested in a more concentrated form. Also, if the dose of vitamin D is administered during the course of the day, as when it is incorporated in an infant's formula, it is more completely utilized than when the daily ration is given in a single dose.

Little is known of the fate of vitamin D after absorption. Apparently, storage of this dietary essential is not great, for even when it is fed to animals in generous amounts there is no appreciable increase in the tissue content of the vitamin. Nor do tissue concentrations bear a significant relation to the vitamin intake (Guerrant and coworkers, 1938). On the other hand, Heymann (1937) showed that after the administration of a single massive oral dose of vitamin D to rabbits (200,000 units) all tissues of the body acquire antirachitic properties. The vitamin is lost from the brain in approximately one week; from other tissues in five to eight weeks; and from the serum in eight to 12 weeks. This long sojourn in the body seems to indicate that vitamin D is not rapidly destroyed by tissues but rather that the vitamin is lost slowly through excretion.

Vitamin D is excreted in the milk and this fluid can be made antirachitic to an appreciable degree by feeding large amounts of vitamin D to a lactating woman. Little is known of other routes of excretion of the vitamin.

Bio-assay and Unitage. Although the chemical structures of many substances possessing vitamin D activity are known, it is impossible to determine vitamin D activity by chemical analysis and one must still rely on bio-assay. The official U.S.P. technic utilizes rats as experimental animals. Rats of prescribed age and weight are depleted of vitamin D on a standard rachitogenic diet over a period of 18 to 25 days, at the end of which time symptoms of rickets are evident. For eight days the animals are then given the preparation to be assayed, rested for two days and killed on the following day. Estimation of the degree of skeletal calcification initiated by the vitamin therapy is then made and the results compared with those obtained on animals receiving a U.S.P. standard reference preparation. One international unit of vitamin D possesses the activity of one mgm of an International Standard Solution of irradiated ergosterol, which in turn is equal in potency to 0.025 microgram of crystalline vitamin D (calciferol). The U.S.P. supplies a Reference Cod Liver Oil which has been carefully assayed against the International Standard and this is the reference standard used in the United States. One U.S.P. unit of vitamin D is the equivalent of one international unit.

Preparations. There are three main types of vitamin D preparations: (1) the fish liver oils in which vitamin D is associated with vitamin A; (2) solutions of irradiated ergosterol which contain vitamin D alone; (3) a group of preparations which consist of fish liver oils to which irradiated ergosterol has been added in order to increase the content of vitamin D.

Cod Liver Oil. The official U.S.P., N.F. and B.P. preparations of cod liver oil have already been listed (page 1276). They must contain a minimum of 85 units of vitamin D per gram. The same minimal strength is required of a cod liver oil for inclusion in the N.N.R. Preparations vary in their vitamin D content, however, and some cod liver oils contain as much as 350 units per gram. Therefore, for accurate dosage, it is necessary to know the strength of the particular brand employed. Cod liver oil is the cheapest source of vitamin D, as well as of vitamin A (page 1276).

Halibut Liver Oil, N.N.R. Although this preparation is 50 times as potent as cod liver oil with respect to vitamin A, it contains only 540 units of vitamin D per gram, or six to seven times as much as is present in cod liver oil. It is therefore much more useful as a vitamin A preparation (page 1276), and is seldom used as such for its vitamin D content.

Percomorph Liver Oil, N.N.R. This oil, extracted from livers of the percomorph, is a potent source of vitamin D as well as vitamin A. It is marketed in a form diluted 50 per cent with cod liver oil, and the final product must contain 8500 units of vitamin D per gram to meet N.N.R. specifications.

Natural Vitamins A and D in Oil, U.S.P. This preparation is described on page 1277.

Burbot Liver Oil, N.N.R. This oil, expressed from the livers of the burbot, contains a minimum of 640 units of vitamin D per gram. It is slightly more potent than halibut liver oil in this respect but contains much less vitamin A. The ratio of vitamin A to D in burbot liver oil is approximately the same as in cod liver oil.

Cod Liver Oil Concentrate, N.N.R. Preparations in this category consist of the unsaponifiable portion of cod liver oil dissolved in an inert oil as a vehicle. They are potent sources of vitamin D and for inclusion in N.N.R. must contain a minimum of 1400 units per gram. Most of the preparations are much more potent, however, and some contain as much as 8500 units of vitamin D per gram. These preparations also contain a large amount of vitamin A.

Cod Liver Oil with Viosterol, N.N.R. This preparation is a cod liver oil to which has been added irradiated ergosterol (viosterol) in order to raise the content of vitamin D. To be included in N.N.R., products must contain sufficient added ergosterol to raise the vitamin D content of the oil to 360 units per gram. Such fortified oils need only contain 850 units of vitamin A per gram.

Halibut Liver Oil with Viosterol, N.N.R. This is a better balanced preparation than halibut liver oil alone, if one desires to administer both vitamins A and D. It has the same content of vitamin A as plain halibut liver oil, but in addition irradiated ergosterol is added to bring the total content of vitamin D to 9000 units per gram.

Activated Ergosterol in Oil, U.S.P. This preparation is made so as to contain 10,000 units of vitamin D per gram. It contains no vitamin A and in this respect differs from all the aforementioned preparations. *Viosterol in Oil,* N.N.R., is the same preparation. *Solution of Calciferol,* B.P., contains 3000 units of vitamin D per gram.

Irradiated ergosterol can also be dissolved in solvents that are miscible with water, and one of these, *propylene glycol,* is commonly employed. A water-miscible preparation is useful in infant feeding because it can be dissolved in the milk or formula. One such preparation is *Drisdol* which contains 10,000 units of vitamin D per gram.

Human Requirements. The human requirements of vitamin D have been reviewed by Jeans and Stearns (1938). These investigators define the requirements for vitamin D as "those amounts which, with ample intakes of calcium and phosphorus and a diet otherwise adequate, assure sufficient retention of calcium and phosphorus to permit (a) normal growth and mineralization of the skeleton and teeth of infants and children, (b) maintenance of bony and dental structures during adult life and (c) a sufficient supply for mother and infant during pregnancy and lactation."

Infants' Requirements. The amount of vitamin D which infants must be given depends upon whether breast milk or an artificial diet is fed. Also, the rate of growth is a factor, for the more rapidly growing infant has a higher requirement. The premature infant on an artificial diet probably needs about 600 to 800 units of vitamin D daily when the vitamin is given in the form of cod liver oil. The normal infant on a cow's milk diet requires from 300 to 400 units. Although the needs of the breast-fed infant are probably less, it is best also to allow the margin of safety afforded by the daily ingestion of 300 to 400 units. Inasmuch as there is evidence that vitamin D given in a more concentrated form than cod liver oil is not as well utilized, the dosages cited should be increased if the more potent vitamin concentrates are employed.

Children's Requirements. Most studies indicate that the daily intake of 300 to 400 units of vitamin D is adequate for children. Although quantitative estimates have not been made of the vitamin requirements during adolescence, it has been suggested by Jeans and Stearns that 400 units per day provide an adequate intake.

Adults' Requirements. The vitamin D requirement of adults has not been ascertained. It has been established that augmenting the dietary intake of vitamin D does not decrease the minimal calcium requirements. Nevertheless, Park (1938) is of the opinion that the inclusion of a small amount of vitamin D in the diet (135 units daily) may be beneficial to those individuals who are exposed but little to the sun.

Pregnancy and Lactation. The vitamin D requirements undoubtedly rise during pregnancy and lactation, periods when the effective utilization of dietary calcium and phosphorus is imperative for maternal health. The greatest need is present during lactation when 800 units of vitamin D should be taken daily. During pregnancy, a smaller amount would probably suffice but a daily intake of 800 units daily is usually recommended.

Therapeutic Uses. The chief therapeutic use of vitamin D is in infant feeding for the *prophylaxis of rickets.* Administration should start at the beginning of the third week of life. The initial dose is 200 units daily. This is increased within a few days to 400 units and by the end of the first month of life to 800 units. These doses are well in excess of the minimal requirements. It is probably advisable to continue the administration of vitamin D throughout the period of growth. The choice of preparations is wide. Plain U.S.P. cod liver oil is probably the least expensive. The one disadvantage of this drug is the difficulty sometimes experienced in administering the large volume required. Although the taste is objectionable to adults, infants, as a rule, become fond of cod liver oil. In favor of cod liver oil is the important fact that the vitamin is in a sufficiently dispersed form to allow fairly complete absorption. Also, the large volume of oil adds many calories to the diet. If a vitamin D concentrate is used, cost is one factor governing choice. It is often desired to administer vitamin A in conjunction with D, a measure which may be extremely beneficial and can in no way be harmful. In such an event, a well-balanced vitamin A and D preparation should be chosen. If it is desired to give vitamin D in milk, a preparation miscible with water must be used.

Premature infants and an occasional full term infant are especially susceptible to rickets. The dose of vitamin D must then be adjusted to meet the individual requirements and it is sometimes necessary to raise the daily intake to as high as 30,000 units in order to prevent the onset of the deficiency disease. Such cases, however, are extremely rare, and usually 800 to 1200 units daily suffice.

The curative dose of vitamin D for the treatment of *fully developed rickets* is larger than the prophylactic dose. The average daily dose is 1200 units, but again this may have to be raised appreciably in certain refractory cases. Indeed, there are reports in the literature of individuals requiring several hundred thousand units, but obstinate cases seldom require more than 50,000 units daily. Backwin and coworkers (1940) reported an interesting case of refractory rickets which required a curative dose of 1,000,000 units and a maintenance dose of 440,000 units. Large doses of vitamin D should also be given when rapid healing is desired, as for example in a severe case of thoracic rickets in which respiration is embarrassed.

Vitamin D is a valuable therapeutic agent in the treatment of *infantile tetany* which is often associated with rickets. Although the immediate symptoms are best controlled by the administration of calcium, and possibly by parathyroid extract in some cases, vitamin D and adequate dietary calcium are used for subsequent therapy to prevent nervous system symptoms and to cure the rickets.

Adult rickets or osteomalacia also calls for vitamin D therapy. This condition is associated with an extreme abnormality either in the dietary content or intestinal absorption of calcium and phosphorus, or in the utilization of these elements. Large doses of vitamin D in conjunction with an improved dietary are indicated.

Vitamin D is also given to aged individuals suffering from *bone fractures.* The purpose is to provide an optimal amount of calcium for proper healing.

There are certain conditions which are known to lead to *poor absorption of vitamin D.* If untreated with vitamin, a frank deficiency may develop. Therefore, vitamin D may be of definite prophylactic value in such disorders as diarrhea, steatorrhea, biliary obstruction, and any other abnormality in gastro-intestinal function in which absorption is appreciably diminished.

Vitamin D in huge doses has been used for a variety of *miscellaneous conditions* in which the rationale of therapy is difficult to understand. Although favorable results have been reported in the treatment of such unrelated conditions as psoriasis, arthritis, hay fever, etc., it is doubtful whether real benefit can be obtained from its use in these disorders.

DIHYDROTACHYSTEROL (A.T. 10)

It was pointed out that the irradiation of ergosterol results in the formation of a series of compounds with different pharmacological properties. Of the series, calciferol (vitamin D_2) is the only member which is antirachitic, the other compounds having an action more like that of the hormone of the parathyroid gland. One of the products of the irradiation of ergosterol is tachysterol. A reduction product of this compound, dihydrotachysterol, has actions which resemble those of the parathyroid hormone so closely that the drug is especially useful in the treatment of parathyroprivic conditions.

Pharmacological Actions. The investigations of Albright and his associates (1938, 1939) have contributed greatly toward a working hypothesis of the mechanism of action of dihydrotachysterol. As was pointed out in the discussion of vitamin D, there are two types of drugs which profoundly influence calcium and phosphorus metabolism. At one extreme are the antirachitic vitamins; at the other, the parathyroid hormone. The hormone of the parathyroid does not affect the absorption of calcium and phosphorus from the intestinal tract, but rather promotes the renal excretion of phosphorus, lowers the phosphate content of the blood and in this way promotes the mobilization of calcium from bone and raises the concentration of serum calcium (*see* also page 1175). Vitamin D, on the other hand, enhances the intestinal absorption of calcium and phosphorus. According to Albright, the vitamin also increases phosphate excretion in the urine to a small extent, and in this manner mobilizes calcium from the osseous tissue, but this is a minor action.

The investigations of Albright have shown that dihydrotachysterol likewise promotes a phosphaturia, thus mobilizing calcium from the skeleton, and enhances intestinal absorption of calcium. The former action of dihydrotachysterol, however, is by far the more prominent, and therefore the drug closely resembles the parathyroid hormone in its actions. At the same time, the compound, to a certain extent, promotes the absorption of calcium. Both types of action are beneficial in the treatment of hypoparathyroidism, as evidenced by the uniformly

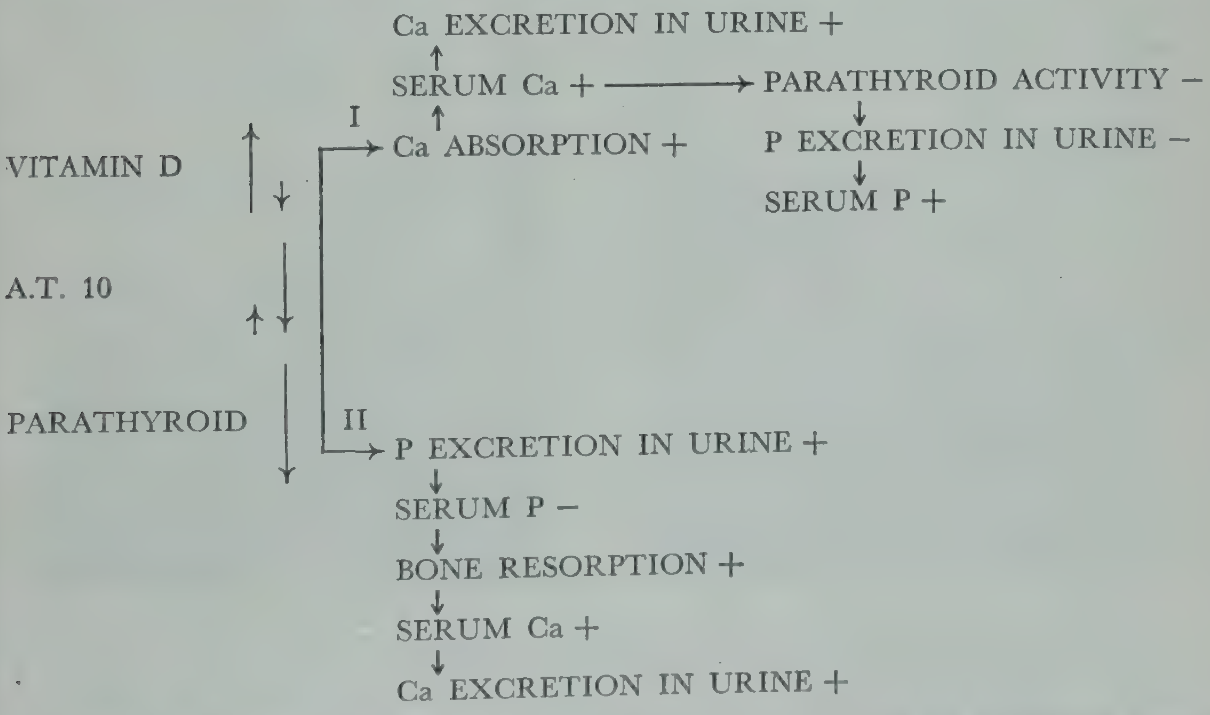


FIGURE 124. *The respective rôles of vitamin D, dihydrotachysterol and parathyroid extract in the metabolism of calcium and phosphorus.*

Direction of arrows indicates the type of action exhibited; size of arrows, the relative intensity of action. Note that the primary effect of vitamin D is on the intestinal absorption of calcium, but that it also to some extent promotes urinary excretion of phosphate and the mobilization of calcium from skeletal stores. Parathyroid affects only the resorption of calcium from bone, probably by enhancing the renal excretion of phosphate. Dihydrotachysterol resembles parathyroid extract more than vitamin D in its mechanism of action. (After Albright, 1938. Courtesy of the *Transactions of the Association of American Physicians.*)

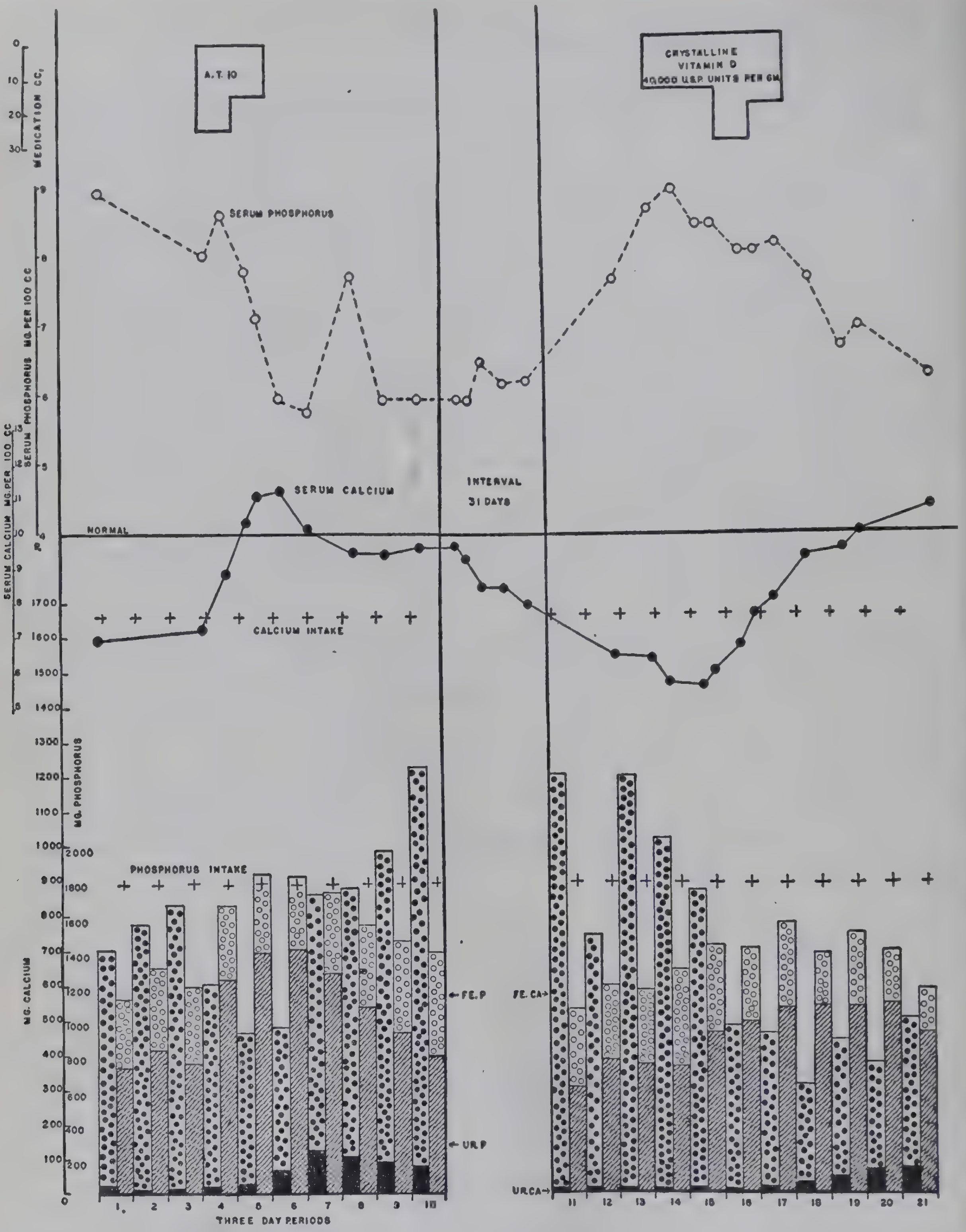


FIGURE 125. *A comparison of the effects of dihydrotachysterol (A.T.10) and vitamin D on calcium and phosphorus metabolism in a patient with severe idiopathic hypoparathyroidism.*

All symbols are explained in the figure. Note the rise in serum calcium and the fall in serum phosphorus toward normal values following the administration of A.T. 10. This was largely the result of the increased urinary excretion of phosphorus, the phosphorus balance becoming slightly negative, and the decreased fecal excretion of calcium. Crystalline vitamin D raised the level of serum calcium and lowered the serum phosphorus in essentially the same manner. The fecal excretion of calcium was diminished and the urinary excretion of phosphorus was increased. Note, however, that the effect of A.T. 10 on the urinary excretion of phosphorus was greater than that of vitamin D, whereas the effect of vitamin D was more prominent in lowering the fecal excretion of calcium (*i.e.*, in promoting intestinal absorption of calcium). Note also that successful clinical results which have attended the use of dihydrotachysterol. The comparative actions of dihydrotachysterol and vitamin D_2 on the intestinal absorption, renal excretion and blood levels of calcium and phosphorus in hypoparathyroidism are illustrated in Figure 125. The relationship between the actions of vitamin D, dihydrotachysterol and the parathyroid hormone is depicted in Figure 124.

The interpretations of Albright as to the mechanism of action of dihydrotachysterol were uniquely confirmed by Shohl and coworkers (1939). These investigators studied the effects of dihydrotachysterol on two types of experimental rickets in rats. They reasoned that although dihydrotachysterol is not effective in the treatment of clinical rickets, it should be beneficial in the treatment of that type of experimental rickets produced by a high-phosphorus low-calcium diet in that the excretion of excess phosphate would be enhanced. On the other hand, dihydrotachysterol should prove particularly unfavorable to the healing of rickets caused by low-phosphorus diets because it would increase the excretion of phosphate needed for deposition in bone. The experimental results confirmed their working hypothesis.

Toxicity. Dihydrotachysterol shares the toxic properties of the parathyroid hormone, and when administered demands that attention be paid to the calcium and phosphorus levels of the blood. Excessive doses have caused polyuria, thirst, nausea, abdominal cramps, vertigo and tinnitus (Rose and Sunderman, 1939), and are capable in experimental animals of inducing metastatic calcification.

Absorption, Fate and Excretion. Dihydrotachysterol, like vitamin D, can be absorbed from the gastro-intestinal tract. Thus, in contrast to parathyroid hormone, it can be given orally and this constitutes one of the advantages of the drug. Dihydrotachysterol is apparently destroyed slowly, its effects being evident for several days. Therefore, during chronic administration, the drug need be given only three times weekly.

Preparations. Dihydrotachysterol (A.T. 10) is not generally available. It can be obtained for experimental purposes from the Department of Medical Research of the Winthrop Chemical Company. It is conveniently dispensed for oral administration in oily solution containing five mgm per cc.

Therapeutic Uses. Dihydrotachysterol is used in the treatment of hypoparathyroidism of idiopathic or postoperative etiology. It is effective in controlling convulsions and in maintaining a normal level of calcium in the blood. It is the opinion of most investigators that dihydrotachysterol offers the most convenient measure for the control of the parathyroprivic patient, and all reports on its use have been favorable. (*See* Albright and associates, 1938, 1939; MacBryde, 1938; Hurxthal and Claiborne, 1939; Margolis and Krause, 1939; Rose and Sunderman, 1939; Eaton and Haines, 1939.)

The indications for the use of dihydrotachysterol are approximately the same as for parathyroid hormone. The drug is by no means innocuous; it is expensive, and is therefore not indicated in those cases than can be controlled by calcium salts and vitamin D. Dihydrotachysterol should not be employed alone, but rather calcium and vitamin D should be given in conjunction and the dose of dihydrotachysterol reduced to the minimum compatible with good therapeutic results.

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the effects of vitamin D are slower in onset and more prolonged than those of A.T. 10. (After Albright, Bloomberg, Drake and Sulkowitch, 1938. Courtesy of the *Journal of Clinical Investigation*.)

The dose of dihydrotachysterol cannot be dogmatically stated, but varies with individual requirements. At the beginning of therapy, it may be necessary to administer large doses (three cc per day) in order to control the tetany. The dose can then be reduced to a maintenance level which usually varies from 0.3 to one cc per day. The maintenance dose may be given three times weekly. The level of blood calcium should be ascertained at intervals in order to determine the adequacy of dosage. Albright (1939) has outlined a simple procedure whereby the patient can adjust his own dosage by following the calcium in the urine (page 1178).

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CHAPTER 73

FAT-SOLUBLE VITAMINS

II. VITAMIN K AND VITAMIN E

VITAMIN K

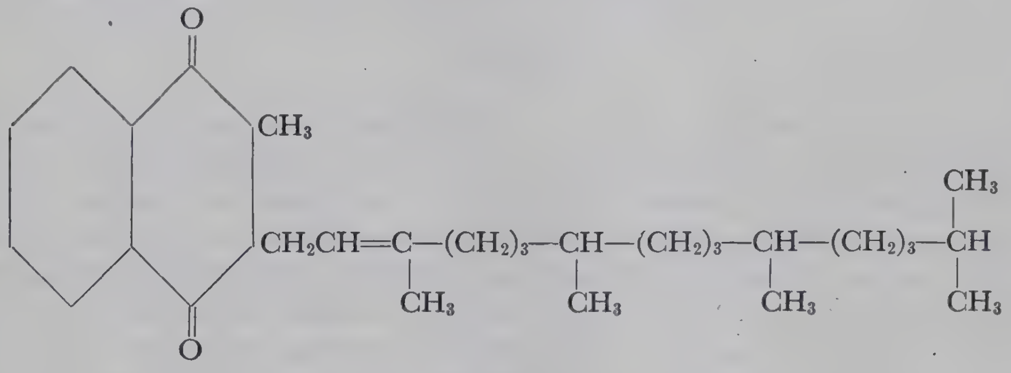
Historical. Vitamin K is a dietary principle which is seemingly essential for the normal clotting of blood. In 1929, Dam observed that chickens fed on inadequate diets developed a deficiency disease in which the outstanding symptom was spontaneous bleeding apparently due to a low content of prothrombin in the blood. In subsequent publications, Dam and coworkers (1935, 1936) reported that although the condition was not cured by any of the known vitamins, it could be rapidly alleviated by feeding an unidentified fat-soluble substance. To this substance Dam gave the name vitamin K ("Koagulation" vitamin). Independently, Almquist and Stokstad (1935) described the same hemorrhagic disease in chickens and the method for its prevention.

The investigations of Dam and Almquist and their respective associates were reported at a time when the attention of several groups of workers was centered on the cause of the hemorrhagic tendency in patients with obstructive jaundice and diseases of the liver. For example, Quick and coworkers (1935) made the pertinent observation that the coagulation defect in jaundiced individuals was due to a decrease in the concentration of prothrombin in the blood. In the same year, Hawkins and Whipple reported that animals with biliary fistulas were likely to develop excessive bleeding. Hawkins and Brinkhous (1936) subsequently showed that this was due to a deficiency in prothrombin and that the condition could be relieved by the feeding of bile salts. Smith, Warner and Brinkhous (1937) further demonstrated that injury to the liver produced by a hepatotoxic agent such as chloroform led to a deficiency in prothrombin and excessive bleeding in experimental animals.

The clinical culmination of these experimental studies came with the demonstration of Butt, Snell and Osterberg (1938) and Warner, Brinkhous and Smith (1938) that combination therapy with vitamin K and bile salts was effective in the treatment of the hemorrhagic diathesis in cases of jaundice. Apparently vitamin K and adequate hepatic function are linked to the physiological mechanisms operating in the normal clotting of blood.

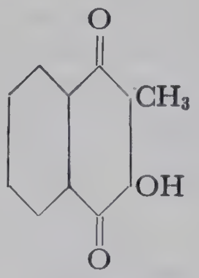
Distribution, Chemistry and Preparations. The early investigations of Dam (1935) and Almquist and Stokstad (1935) showed that vitamin K was a fat-soluble substance present in the unsaponifiable, non-sterol fraction of hog-liver fat, and in alfalfa. Subsequently it has been demonstrated that the vitamin is present in the photosynthetic portion of plants and in many vegetable oils. The feces of most species of animals contain large amounts of the vitamin which probably is formed by the action of bacteria in the intestinal tract. Putrefied protein, such as fish meal and casein, is also an excellent source of vitamin K. Concentrates made from alfalfa were extensively employed in the early use of vitamin K.

The elucidation of the chemical structure of vitamin K came with startling swiftness. By 1938, Thayer and coworkers had isolated a crystalline material, possessing high vitamin K activity, which contained a quinone structure. Soon it was appreciated that vitamin K was not a single compound but occurred naturally in the form of at least two distinct substances which were designated as vitamin K_1 and K_2. Both are derivatives of naphthoquinine. Their structure has been determined and the synthesis of vitamin K_1 has been accomplished (MacCorquodale and coworkers, 1939; Fieser, 1939; Binkley and coworkers, 1940). Vitamin K_1 is 2-methyl-3-phytyl-1, 4-naphthoquinone.



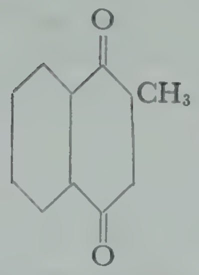
Vitamin K_1

In the meantime, Almquist and Klose (1939) demonstrated that phthiocol, a quinone derivative so named because it was first isolated from human tubercle bacilli by Anderson and Newman (1933) and later synthesized by them, possessed vitamin K activity. Almquist and Klose stated that they believed phthiocol to be the simplest member of a homologous series of antihemorrhagic substances. Their prediction was almost immediately fulfilled, and soon there appeared a large number of publications of various investigators reporting on the vitamin K activity of scores of quinone derivatives. Phthiocol has the following structural formula:



Phthiocol

The comparative activity of the various natural and synthetic compounds possessing vitamin K activity cannot be stated with certainty. Phthiocol is much less active than crystalline preparations of the natural vitamin. However, a large number of synthetic quinone derivatives approach or exceed the potency of the natural vitamin. Outstanding among these is 2-methyl-1, 4-naphthoquinone. This compound possesses outstanding activity, being several times more potent than natural vitamin K_1. Two-methyl-1, 4-naphthoquinone, which has been proposed as a desirable reference substance for defining the unit of vitamin K activity, has the following structural formula:



2-methyl-1, 4-naphthoquinone

Chemical progress has had repercussions in the clinical field. In most of the basic clinical investigations on vitamin K, vitamin concentrates of alfalfa were employed. Such preparations are adequate for oral administration, but are unsuitable for injection. On the other hand, synthetic quinone derivatives are simple to prepare and consequently inexpensive, do not require bio-assay, can be easily adjusted with regard to dosage, can be given by any route, and have largely replaced crude concentrates. Two-methyl-1, 4-naphthoquinone, the most active of the synthetic substitutes for vitamin K, has received extensive clinical trial (*see* Aggeler and coworkers, 1940; Allen and Julian, 1940; Andrus and Lord, 1940; Butt and coworkers, 1940; Rhoads and Fliegelman, 1940). The compound may be given orally in conjunction with bile salts, or by intramuscular injection in solution in oil. It is insoluble in water. The toxic dose of 2-methyl-1, 4-naphthoquinone is several hundred times as great as the therapeutic dose. Crystalline vitamin K_1 has no demonstrable toxicity (Molitor and Robinson, 1940).

For intravenous administration it is essential to have a water-soluble preparation. Many of these have been prepared and several have been demonstrated to be as active as 2-methyl-1, 4-naphthoquinone (Richert and coworkers, 1940). It has been shown experimentally that water-soluble vitamin K substitutes can be absorbed from the gastro-intestinal tract in the absence of bile (Warner and Flynn, 1940). If this observation receives clinical corroboration, the preparation of choice for vitamin K therapy may ultimately be one of the water-soluble group.

Physiological Function. Although all investigators are not in agreement as to the exact mechanism involved in the clotting of blood, it is generally accepted that four essentials are necessary for this reaction to take place. These are prothrombin, thromboplastin, calcium and fibrinogen. In their simplest form, the reactions which occur when blood clots may be expressed as follows:

$$\text{Prothrombin} + \text{Thromboplastin} + \text{Ca} \rightarrow \text{Thrombin}$$
$$\text{Thrombin} + \text{Fibrinogen} \rightarrow \text{Fibrin}$$

A hemorrhagic diathesis may result from the failure of any one of these factors required for the normal clotting of blood.

The rôle which prothrombin plays in the etiology of certain hemorrhagic diseases was not appreciated until methods were devised for the accurate determination of the prothrombin content of the blood. The method of Quick and coworkers (1935, 1937, 1938) has been widely applied and is simple. In brief it is based upon the principle that if thromboplastin and calcium are added in optimal amounts to blood of normal fibrinogen content the only factor that can vary the clotting time is an inadequate concentration of prothrombin. In the method of Quick, shed blood is immediately decalcified with oxalate solution to prevent clotting. Following this, ionized calcium ($CaCl_2$ solution) and thromboplastin (suspension of rabbit brain) are added simultaneously. Human blood with a normal content of prothrombin clots in approximately 12 to 20 seconds following such a procedure. Blood with only 20 per cent of the normal prothrombin content clots within 25 to 30 seconds. If the prothrombin content is further reduced, clotting time is greatly prolonged. Thus a test of clotting time can detect only a severe deficiency.

Inasmuch as a hemorrhagic diathesis in jaundiced individuals, in animals with biliary fistulas or damaged livers, and in vitamin K-deficient chickens is associated, in each instance, with an inadequate concentration of prothrombin in the blood, a common causative factor is probable. There is increasing evidence that a deficiency of vitamin K accompanies all the aforementioned conditions.

The question immediately arises how a deficiency of a substance which is so ubiquitous in distribution as vitamin K and which apparently is formed by bacteria in the intestinal tract can exist. The probable explanation is that in the absence of bile, fat-soluble vitamin K is not absorbed from the intestinal tract. There is convincing indirect evidence in support of this concept. It is well known that in the absence of bile the absorption of other fat-soluble vitamins, especially carotene, is impeded. Also it has been demonstrated that the feeding of bile salts to an individual with obstructive jaundice and a prothrombin deficiency can correct an abnormal clotting time. Still more effective, however, is the combined feeding of bile salts and vitamin K. Lastly, the oral administration of vitamin K alone is ineffective for the defect in absorption has not been overcome (*see* Figure 126). Direct proof that the intestinal absorption of vitamin K is impaired in the absence of bile must await chemical methods for the quantitative determination of the vitamin.

The exact rôle of vitamin K in the clotting of blood has not yet been explained. Seemingly it is a substance essential to the formation of prothrombin. Presumably the site of action of the vitamin is in the liver, for it does not affect the clotting time if added *in vitro* to blood deficient in prothrombin or if administered to hepatectomized animals (Andrus and coworkers, 1939). The normal liver can produce prothrombin in the presence of an adequate amount of vitamin K; but, if the liver tissue is seriously damaged, or in the absence of the vitamin, prothrombin apparently cannot be formed in amounts sufficient to maintain clotting time. If the clotting defect is due to a vitamin K deficiency, therapy with the vitamin is specific and the effect on the delayed clotting time is striking. If, on the other hand, the low prothrombin level of the blood is the result of extensive damage to hepatic cells, vitamin therapy is ineffective. Thus hypoprothrombinemia due to chronic injury to the liver by chloroform is not influenced by the administration of vitamin K because the excess of vitamin does not compensate for the injury to the hepatic cells (Brinkhous and Warner, 1940). Neither is vitamin K effective in clinical conditions in which delayed clotting time is due to advanced cirrhosis or other types of hepatic disease associated with functional insufficiency (Aggeler and coworkers, 1940; Andrus and Lord, 1940; Rhoads and Lee, 1940; Allen and Julian, 1940; Pohle and Stewart, 1940).

Bio-assay and Unitage. There is no official method for the bio-assay of vitamin K and therefore the activity of various preparations is expressed in units arbitrarily selected by individual investigators. The method of assay and unit of potency devised by Dam and Glavind (1938) have probably been more widely used than any other. Dam defines a unit as the smallest amount of vitamin K, per gram of chick per day, capable of producing normal coagulability in the blood of avitaminotic chicks after three days of oral administration. Ansbacher (1939) has devised a method of chick assay which requires only six hours. The status of the unit and the methods of assay were reviewed by Snell and Butt (1939).

Absorption and Routes of Administration. Vitamin K is readily absorbed from the normal intestinal tract provided bile salts are present. In the clinical use of concentrates or synthetic substitutes, the oral route of administration is preferred and the vitamin is always given simultaneously with bile salts. The possibility that water-soluble substances having vitamin K activity may be absorbed in the absence of bile has already been discussed. The parenteral administration of synthetic quinones possessing vitamin K activity, however, is also an effective therapeutic procedure and a rapid rise in the prothrombin content of the blood follows their intramuscular or intravenous injection (Figure 126).

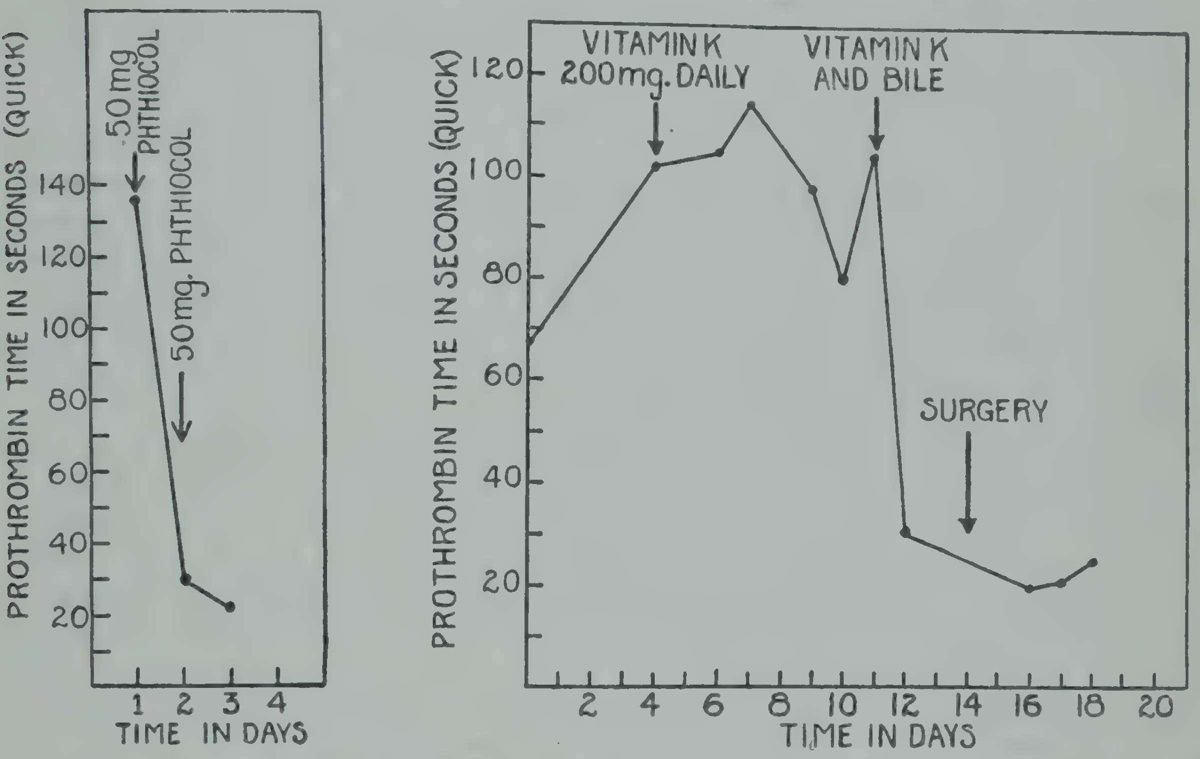


FIGURE 126. *The effect of vitamin K on the prothrombin clotting time in patients with the hemorrhagic diathesis of obstructive jaundice.*

Left: Effect of the intravenous administration of phthiocol to a patient with hypoprothrombinemia associated with carcinoma of the liver and intense jaundice. *Right:* Comparison of the effects of the oral administration of vitamin K with and without bile salts. Patient with obstructive jaundice and not taking food by mouth. The daily administration of vitamin K alone for nearly a week had no significant effect on the prothrombin clotting time. When the same dose of vitamin was given with bile salts a prompt fall to normal in the prothrombin clotting time occurred. (After Butt, Snell and Osterberg, 1938, 1939. Courtesy of the Division of Publications, Mayo Clinic.)

Therapeutic Uses. Vitamin K is useful only in those hemorrhagic conditions in which the abnormal bleeding is due to a low concentration of prothrombin in the blood that is not occasioned by injury to hepatic cells. This limits the application of the vitamin to treatment of the hemorrhagic diathesis of certain types of hepatic and biliary disease and the rarer cases of vitamin K deficiency due to faulty diet or absorption defects other than those caused by a loss of bile. With a simple method available for the determination of prothrombin clotting time, and an effective therapeutic measure provided for raising the prothrombin level of the blood, the control of bleeding in jaundiced patients is no longer the difficult problem that it was, and blood transfusion is seldom required.

Vitamin K should be used prophylactically in all jaundiced patients for whom surgery is planned, even if the prothrombin content of the blood is normal. An adequate oral prophylactic dose of 2-methyl-1, 4-naphthoquinone is one to two mgm daily in addition to one to two grams of bile salts. Medication should be given for a few days prior to operation. In the event that the prothrombin content of the blood is low, the dose may be increased to as high as five mgm daily plus two to four grams of bile salts. Usually the prothrombin content of the blood returns to normal after one or two administrations of the vitamin. If oral therapy is not feasible, 2-methyl-1, 4-naphthoquinone in oily solution may be given by intramuscular injection in the dose of two to four mgm. A single dose is effective for from several days to a week.

Vitamin K should also be used postoperatively, especially if the prothrombin content of the blood was low before operation. Otherwise it is necessary only to follow the prothrombin clotting time and administer the vitamin if there is specific indication that the prothrombin content of the blood is falling.

The treatment of a patient during active hemorrhage is more difficult. The transfusion of blood accomplishes the dual purpose of combating shock and furnishing an immediate supply of prothrombin. "Bank blood" should not be employed as the prothrombin content steadily diminishes upon standing (Rhoads and Panzer, 1939; Quick, 1940). Vitamin K and bile salts should then be given. If gastro-intestinal bleeding has occurred, it may be necessary to lavage the intestinal tract free of clotted blood in order that adequate absorption may take place, or to resort to parenteral therapy.

Brinkhous and coworkers (1937) showed that the prothrombin clotting time of newborn infants is much longer than that of the normal adult. In hemorrhagic diseases of the newborn, the prothrombin level of the blood may be only five per cent of the normal adult level. Furthermore, Waddell and Guerry (1939) demonstrated that an abnormally long prothrombin clotting time in infants can be returned approximately to normal within 90 minutes by the oral administration of two cc of a concentrate of vitamin K. They suggested that the vitamin may be a valuable therapeutic agent in the treatment of hemorrhagic diseases of the newborn. Also the administration of vitamin K to pregnant women two to four weeks prior to delivery significantly raises the prothrombin content of the blood of the newborn infant (Hellman and Shettles, 1939). These observations have been abundantly confirmed and extended (Kato and Poncher, 1940; Shettles and coworkers, 1939; Hellman and coworkers, 1940; MacPherson and coworkers, 1940; Grossman, 1940). The prothrombin level of infant's blood often falls after birth and this may be due to the absence of a normal intestinal bacterial flora (Quick and Grossman, 1940). Compounds possessing vitamin K activity can easily and safely be administered to infants, either in their formula, as a special supplement, or by injection. The prophylactic use of vitamin K during the first few weeks of life and possibly during the late stages of pregnancy has been recommended as a sound procedure to reduce the danger and incidence of hemorrhagic diseases of the newborn. Also as a therapeutic measure, the administration of compounds possessing vitamin K activity rapidly arrests hemorrhage and relieves symptoms. Thus Poncher and Kato (1940) have reported successful results in the treatment of hemorrhagic disease of the newborn after the oral administration of 10 mgm of 2 methyl-1, 4-naphthoquinone or the subcutaneous or intramuscular injection of one or two mgm of a corresponding water-soluble preparation.

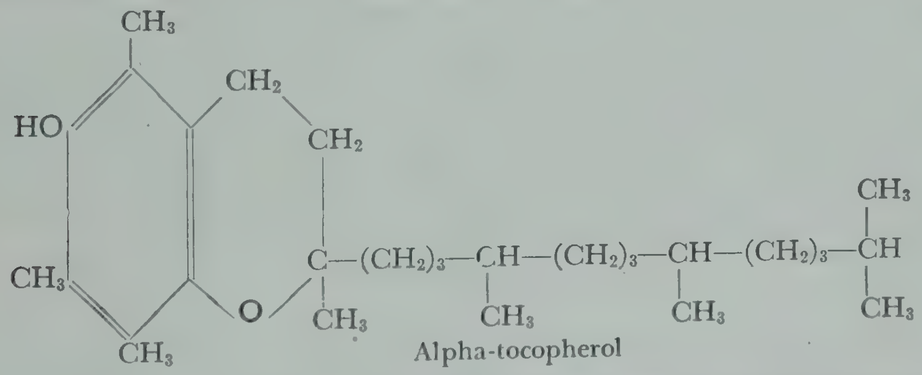
Vitamin K is ineffective in hemophilia, a disease which is not associated with a deficiency of prothrombin. Neither has it been efficacious in the treatment of such conditions as menorrhagia, metrorrhagia and essential hematuria (Butt, Snell and Osterberg, 1938, 1939). It may prove effective, however, in hemorrhagic conditions associated with a low prothrombin content of the blood in which diarrhea or functional defects of the bowel prevent adequate absorption of the vitamin. These conditions include sprue, chronic ulcerative colitis and intestinal short-circuiting and obstruction (Clark and associates, 1939).

VITAMIN E

The existence of vitamin E was first announced by Evans and Bishop in 1922. These investigators were studying the effects of diet on the ovulatory rhythm and reproduction of rats. They found that animals, subsisting on a diet complete in all dietary essentials then recognized, ovulated and conceived normally; but at some time during the period of gestation death and resorption of the fetuses occurred. The same animals could experience a normal gestation period if fed such foods as fresh lettuce leaves or whole wheat. The unknown dietary principle essential for normal gestation was first designated as vitamin X and then changed to vitamin E, the vitamin alphabet at that time having progressed only as far as D. The observations of Evans were soon confirmed by Mattill and Stone (1923), and Sure (1924), and were extended by Beard (1926) to include mice.

Chemistry. It was evident early that vitamin E was a fat-soluble substance susceptible to oxidation in rancid fats and oils. Indeed, one of the most effective means of preparing a diet deficient in vitamin E is to incorporate slightly rancid fats in the dietary mixture. One of the best sources of the vitamin was found to be wheat germ oil, for the reason that the oil contains anti-oxidants. This readily available source provided the stimulus for extensive chemical studies of the vitamin which have been summarized by Evans (1932), Mattill, (1938) and Nelson and Tolle (1939). The culmination of the chemical investigations of many groups of workers was the isolation by Evans, Emerson and Emerson (1936), and Emerson, Emerson, Mohammad and Evans (1937) of three related alcohols possessing the biological activity of the vitamin. To these substances have been given the names alpha, beta and gamma tocopherol. Alpha-tocopherol possesses the greatest activity; but, as is the case with the other fat-soluble vitamins, vitamin E must be regarded as existing in multiple forms.

The chemical structure of the tocopherols was soon elucidated. Alpha-tocopherol is a chroman derivative to which Fernholtz (1938) assigned the following structural formula:



Alpha-tocopherol

Karrer and associates (1938) synthesized alpha-tocopherol and the synthetic compound is indistinguishable from that occurring in nature.

Information has accumulated on the relation between the chemical structure and biological activity of compounds possessing vitamin E activity. The side-chain can be altered little before biological activity is lost. Also the methyl groups in the benzene ring are important. Although many compounds of simpler structure than the tocopherols have been shown to possess vitamin activity, none compares with alpha-tocopherol in potency.

Physiological Functions and Symptoms of Deficiency. Little is known of the manner in which vitamin E functions in the body and all information must be deduced from the symptoms of deficiency. The majority of experiments have been conducted on rodents, and whether vitamin E is essential in human nutrition is not known. The female rat on a diet deficient in vitamin E shows no abnormality until gestation is well advanced. Estrus, ovulation and impregnation are normal and gestation proceeds uneventfully until about the tenth day. At that time, according to Urner (1931), a rarefaction of the mesenchyme and a failure of the blood-forming tissues of the fetus occur. The malnourished embryo dies and is resorbed. The administration of a single large dose of vitamin E as late as the fifth day of pregnancy assures a normal gestation.

In the male rat, vitamin E deficiency is of more serious consequence, resulting in degenerative changes in the germinal epithelium. Diminutive tubules containing only the cells of Sertoli remain after continued deficiency, and the process is then irreversible, vitamin E therapy being of little avail.

Species Variation. The fowl is the only species other than the rat in which vitamin E has been proved to be essential for fertility. The vitamin E content of the eggs and of the food of hens can be directly correlated with each other and with the hatchability of the eggs. Death of the embryo is due to a disintegration of the blood vessels of the blastoderm. Cognizance is taken of the vitamin E content of the diet in commercial poultry raising. Reproduction in goats and rabbits is not seriously affected by absence of the vitamin. It is reported that sterility in cows and also in human beings has been overcome by the administration of wheat germ oil, but the true significance of these results is difficult to evaluate.

Striate Muscle. A diet deficient in vitamin E leads to muscular dystrophy in rats, rabbits and guinea pigs, an observation that was made by many investigators (Goettsch and Ritzmann, 1939; MacKenzie and McCollum, 1939; Morris, 1939; Shimotori, Emerson and Evans, 1939). The muscular dystrophy can be cured in a striking manner by the use of alpha-tocopherol and by wheat germ oil. A fact that is difficult to explain, however, is that oxidized wheat germ oil, which is devoid of the antisterility factor, can nevertheless cure muscular lesions (Goettsch and Ritzmann, 1939).

Absorption, Distribution and Fate. Vitamin E is readily absorbed from the intestinal tract. It is generally distributed in the fat and skeletal muscles of animals subsisting on an adequate diet, but is absent from the tissues of deficient animals. The vitamin is effectively stored and an animal previously subsisting on an adequate diet and then fed a diet deficient in vitamin E may have several normal pregnancies before the deficiency becomes apparent. Seemingly the utilization of the vitamin is not increased by pregnancy.

Preparations. Preparations of vitamin E are not official or included in the N.N.R. Both wheat germ oil and alpha-tocopherol, however, can be obtained for experimental purposes.

Therapeutic Uses. Inasmuch as there is no proof that vitamin E is essential in human nutrition, therapeutic applications of the vitamin have been few, and mainly experimental in nature. Watson (1936) and Currie (1936) reported successful results in the treatment of *habitual abortion* with wheat germ oil. Also there have been reports of the successful use of the vitamin in the treatment of *muscular dystrophies* (Bicknell, 1940; Stone, 1940) and *amyotrophic lateral sclerosis* (Wechsler, 1940). Further information is necessary to establish the value of the vitamin in therapy. The status of vitamin E, especially in regard to the treatment of habitual abortion, has been reviewed by the Council (1940).

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APPENDIX

PRINCIPLES OF PRESCRIPTION WRITING

A *prescription* by strict definition is a physician's written order to a pharmacist for medicinal substances for a patient. It includes directions to the pharmacist regarding the preparation and to the patient regarding the use of the medicine.

In reality, however, a prescription is infinitely more than can be simply defined. It is a summary of the physician's diagnosis, prognosis and treatment of the patient's illness. It brings to a focus on one slip of paper the diagnostic acumen and therapeutic proficiency of the physician. The prescription is truly the ultimate step in the application of pharmacology to clinical medicine, and combines the knowledge of the absorption, fate, excretion, action, toxicology and dosage of drugs with the requirements for restoration of the patient to health.

Unfortunately, prescription writing is a neglected art both in medical practice and in the medical school curriculum. This is largely due to the welcome disappearance of the polypharmacal monstrosity known as the "shot-gun" prescription. Thirty years ago it was not unusual for a score or more of ingredients to be ordered in the same mixture. Prescriptions today are considered quite elaborate if they contain more than four or five drugs, and often they contain only one or two. This improvement is directly due to the development of more rational therapeutics. It is interesting to recall that Sir William Osler, who was termed a "therapeutic nihilist," was in reality one of the early advocates of a rational type of therapy and routinely wrote prescriptions that possessed the accuracy and simplicity for which we strive today. The tendency toward simplicity, however, has an unfortunate aspect in the neglect of the art of prescription writing. Some physicians are careless in constructing their orders to pharmacists, and others often employ proprietary preparations for which no prescription is necessary other than the writing of the patented name on a slip of paper.

An abundant knowledge of pharmacology would be of little practical value to the physician if he were unable to incorporate it in prescriptions for his patients. To be able accurately and speedily to write prescriptions considerable practice is necessary. The prescription should be written legibly. If one has a poor handwriting, the prescription should be printed or typewritten. Some physicians appear to enjoy using their own systems of hieroglyphics instead of legitimate letters of the alphabet. If the purpose of this is to keep the prescription a secret from the patient, an object of doubtful desirability, it also succeeds on occasion in keeping it a secret from the pharmacist. Prescription pads supplied by drug firms or pharmacists and bearing advertising material should be avoided. It is convenient and the accepted form to have one's name, address, telephone number, office hours and narcotic registry number printed on the prescription blank. Because of the fact that at any time prescriptions may become medicolegal documents, they should be written in ink, although this is compulsory only for narcotic orders. It is also an excellent custom, too infrequently followed, for the doctor to keep an exact or carbon copy for his files. This copy protects him and serves to complete the record of treatment.

The actual writing of a prescription, if possible, should be done in the presence of the patient. This tends to impress upon him that the prescription is being written for his particular illness and increases his confidence in the physician. One should write without hesitation and with a degree of determination, concentration and celerity indicative of the fact that the writer is perfectly acquainted with what he is doing. Erasing, crossing out and tearing up a prescription in the presence of the patient are poor procedures psychologically and should be avoided. The prescription should be laid aside for a few minutes and then proofread before affixing one's signature. This is important because errors do occur, especially if the physician has been distracted by talkative patients or relatives.

Choice of Language. Prescriptions were formerly written in Latin and many physicians still observe this custom. Within recent years, however, there has been a concerted movement in medical school teaching and medical writing away from the use of Latin in prescriptions. The reasons for this are many and the question is sufficiently important briefly to review the pros and cons.

Arguments in Favor of the Latin Form. It has been said that Latin provides an unchanging form which can be interpreted all over the world. Historically, Latin is the language of science and the Latin prescription has become a part of medical tradition. Latin allows for a certain degree of secrecy which may be desirable to maintain toward the laity. Secrecy may be especially desired if patients have prejudices or misconceptions concerning drugs.

Arguments in Favor of the English Form. The Latin nomenclature is far from being constant. Changes in terminology are made at each pharmacopeial convention. If the prescription were written in classical Latin and contained somewhat unusual directions, the pharmacist would be unable to translate it. The coining of Latin names for new drugs is often a difficult matter. If one desires secrecy, it is hardly obtainable with Latin prescriptions because Latin and English terms are so much alike. Furthermore, the increasing medical intelligence of the laity allows cooperation between patients and physicians in which secrecy has no part. Few physicians are sufficiently trained in Latin to write prescriptions which are grammatically correct. The unwillingness to write in Latin increases the tendency to avoid the issue by writing for proprietary drugs. Prescription writing in Latin is a bugbear to the medical student and there are more urgent demands on his time. Studies have shown that the hours and effort spent in mastering this formality were poorly invested. The English form is the preferred one of many leading medical journals and is now also official in the U. S. Pharmacopeia.

In the belief that the arguments against Latin are convincing and that prescriptions correctly written in English are preferable to those incorrectly written in Latin, the English form is used throughout this text. Sufficient Latin is included in this section to enable the student to interpret the writing of those who still prefer the old method and to appreciate the efficiency of the newer system.

Choice of a System of Weights and Measures. Unfortunately, the tendency to use apothecaries' weights and measures in prescriptions has persisted even more tenaciously than the Latin form. The burden of a binominal system, metric and apothecary, is evident to all. It is confusing, wasteful and occasionally leads to serious error. The metric system is greatly to be preferred. It is a self-explanatory decimal system, is employed throughout the scientific world and is official in the U.S.P. The metric system simplifies the calculation of dosage because both the terms for weight and measure—the gram and the cubic centimeter—are based on a common unit, the meter. The gram and the cubic centimeter for practical purposes are nearly always interchangeable. The apothecaries' system, not being a decimal system, does not allow for simplicity of calculation, and by tradition employs Roman numerals and archaic symbols.

Metrology. *The Metric System.* The *cubic centimeter* (*cc*) is the unit of measure, and is equal to $\frac{1}{1000}$ part of a liter, the content of a cube measuring 10 centimeters on each edge. The *gram* (*Gm.*) is the unit of weight in the metric system and is equal to the weight of 1.0 cc of distilled water at 4.0 C. *in vacuo.* The weights and measures of the metric system are given in Table 61.

In the metric system only Arabic numbers are used. The English or the Latin form may be employed with metric units. In the United States, fluids are measured and solids are weighed, and ordinarily no attention is paid to differences in specific gravity of fluids. This is preferable to the European custom of weighing both solids and liquids, because the patient ultimately measures and does not weigh his dose of liquid medicine. It is necessary, therefore, only to designate amounts of drug by numbers without writing "Gm." or "cc" after the numerals. The official U.S.P. abbreviation for the gram is written "Gm." in order to avoid confusion with the abbreviation for the grain, "gr."

In the prescription itself, the Arabic number is placed after the official name of the drug and if several ingredients are prescribed the decimal points are placed in the same vertical line. Many physicians substitute a drawn line for decimal points and this "decimal line" may be printed on the prescription pad. Above this line one may place "Gm. or cc." although this is not necessary inasmuch as the decimal line presupposes the metric system. An example of the body of a prescription written in the metric form appears as follows:

(No. 1)

℞

Sodium Bromide	20	0
Sodium Barbital	5	0
Syrup of Orange	60	0
Syrup of Cherry, to make	120	0
M.		

Apothecaries' or Troy System. This system must be learned because it is still used by many, and one should be facile at the interconversion of metric and apothecaries' units (see Table 62). The apothecaries' system is also official in the U.S.P. The weights and measures employed are given in Table 61. Roman numerals are used in the apothecaries' system, and numbers *follow* the symbols, thus: ♏xv, ʒv, ℥xiv, etc. When the numeral "one" occurs, it is best to place a dot over it (i) so that the "dots" serve as a check against error, as follows: ℥iv, ʒiij, gr. xiv, etc. When the numeral "one" occurs alone or as the final figure it is written as j instead of i, as follows: ♏xviij, ʒiij, ℥xij. Some use a line over the numerals, as follows: ʒi̅v̅, ℥i̅i̅j̅. The matter of fractions presents variations. The fraction one-half (½) is written ss or s̅s̅, the abbreviation of the Latin "semis," as follows: ʒs̅s̅, ℥i̅s̅s̅; ʒvss; gr. ss. Other fractions are expressed in Arabic, not Roman figures, as follows: gr. 1/10; gr. 1/150; gr. 1/450. Decimal fractions, such as gr. 0.1, are not used. It is not necessary to prefix the word "fluid" (fl) before the units of liquid measures.

TABLE 61

WEIGHTS AND MEASURES

METRIC SYSTEM

Mass

1000	grams	=	*kilogram	(Kg.)
100	grams	=	hectogram	(Hg.)
10	grams	=	dekagram	(Dkg.)
*1.0	gram	=		(Gm.)
0.1	gram	=	decigram	(dg.)
0.01	gram	=	centigram	(cg.)
0.001	gram	=	*milligram	(mg.)
0.000001	gram	=	microgram	(μg.) (γ)

Capacity

1000	cubic centimeters	=	*liter	(L.)
100	cubic centimeters	=	deciliter	(dl.)
10	cubic centimeters	=	centiliter	(cl.)
*1.0	cubic centimeter	=	milliliter	(ml., cc.)
0.001	cubic centimeter	=	microliter cubic millimeter	(μl.) (cmm.)

APOTHECARIES' SYSTEM

Mass

*1	grain	=		(gr.)
20	grains	=	one scruple	(℈)
60	grains	=	*one dram	(ʒ)
480	grains (8 drams)	=	*one ounce, Troy	(℥)
5760	grains (12 ounces)	=	one pound, Troy	(lb.)

Capacity

	*minim	=		(min. or ♏)
60	minims	=	*fluiddram	(fl. dr., ʒ)
480	minims (8 fl. drams)	=	*fluidounce	(fl. oz., ℥)
7680	minims (16 fl. oz.)	=	pint	(pt., O)
32	fluid ounces	=	quart	(qt.)

* Commonly employed units.

When the apothecaries' system is used, the prescription must be written in Latin to meet the requirements of best form. An example of the body of a prescription written in the apothecaries' system for the same ingredients as those in prescription No. 1 is as follows:

(No. 2)

℞
Sodii Bromidi ʒv
Sodii Barbitali ʒj gr. xvj
Syrupi Aurantii ʒij
Syrupi Prunii
Virginianae, q.s. ad ℥iv
M.

Household Measures. Unfortunately, the drugs prescribed so carefully by the physician in milligrams and cubic centimeters are measured by the patient with convenient kitchen utensils. Therefore the physician must know the approximate contents of the various household measures which his patient is likely to employ. These are given in Table 63. The physician should check the utensils employed, or select them himself. Graduated medicine glasses are far superior.

TABLE 62

METRIC AND APOTHECARIES' EQUIVALENTS†

1 milligram	=	1/65	grain	(1/60)
1 gram	=	15.43	grains	(15)
1 kilogram	=	2.20	pounds	[avoirdupois]
		2.68	pounds	[Troy]
1 cubic centimeter	=	16.23	minims	(15)
1 liter	=	1.06	quarts	(1+)
		33.8	fluid ounces	(34)
1 grain	=	0.065	gram	(60 mgm)
1 dram	=	3.9	grams	(4−)
1 ounce	=	31.1	grams	(30+)
1 minim	=	0.062	cc	(0.06)
1 fluiddram	=	3.7	cc	(4−)
1 fluidounce	=	29.57	cc	(30−)
1 pint	=	473.2	cc	(500−)
1 quart	=	946.4	cc	(1000−)

† Figures in parentheses are commonly employed approximate values.

TABLE 63

HOUSEHOLD MEASURES

	Approximate Equivalents	
Measure	Metric	Apothecaries'
1 drop*	1/20 cc	1 minim
1 teaspoon*	5 cc	1+ dram
1 dessertspoon	8 cc	2 drams
1 tablespoon	15 cc	½ ounce
1 wineglass	60 cc	2 ounces
1 glass	250 cc	8 ounces

* See text.

The "drop" presents a special problem. It is not synonymous with the minim, as many believe. Obviously its size depends on the particular fluid being dropped, its specific gravity, temperature, viscosity, etc., and the orifice of the dropper. Luten examined various droppers dispensed with Tr. of Digitalis at drug stores in St. Louis and found that 60 minims of the tincture equaled from 98 to 330 "drops." Obviously, the "drop" is not a fixed amount and the doses of potent drugs should not be prescribed or measured in drops. If medicine droppers are to be used and exact dosage obtained, standardized droppers should be ordered. The U.S.P. standardizes a dropper of such size (external diameter at delivery end equals three mm) that it delivers 20 drops of distilled water weighing one gram at 15 C., the equivalent of one cc or 15 minims. It delivers 80 drops of water to the dram, and about 160 drops of strongly alcoholic liquids (such as Tr. of Digitalis) to the dram. The U.S.P. does not sanction the prescribing of doses in drops, but provides this standard dropper for those who wish to use it. On the other hand, directions for taking a certain number of minims of a drug are useless unless the physician also orders a minim glass for accurate measurement and the patient has sufficient intelligence to use it properly. The druggist is often of considerable help in marking medicine droppers to deliver the desired amount of a drug.

It must also be pointed out that the capacity of a teaspoon is not necessarily four cc (ʒj), as believed by many. Teaspoons vary, and by actual measurement may hold from 3.8

cc to 7.8 cc. A fairly accurate approximation is five cc. Therefore a prescription calling for 100 cc should be considered as containing 20 teaspoon doses, not 25 doses. This point is of practical importance because the patient may obtain only six or less teaspoon doses of drug from an ounce bottle of medicine whereas the physician may have planned it to contain eight doses of one dram each.

Finally, it may be mentioned that the average pharmacist's balance is not accurate for less than 0.006 gram (gr. 1/10). Drugs which are given in fractions of a milligram are usually dispensed in accurately manufactured pills, tablets, etc.

Construction of the Prescription. Traditionally the prescription has four parts.

Superscription. The superscription consists of the patient's name and address, and the date. The age may be included, especially if the patient is a minor. The patient's illness must also in some way be indicated if the prescription is for a drug coming under the Federal Narcotic Regulations. This can be done without revealing the diagnosis by using such phrases as "for pain," "for cough," etc. and these may be inserted in the signature rather than in the superscription, if desired (*see* prescription No. 4). The pharmacist should place the name of the patient on the bottle or container exactly as the doctor has written it in the superscription. This is important if there is more than one patient in a family, and is also a check on the pharmacist in case the wrong container is dispensed or a wrong label attached.

The superscription also includes the symbol "℞," an abbreviation for "recipe," the Latin for "take thou." The stroke after the R has received attention; some believe it is an abbreviation; others consider it the ancient invocation of Chaldean physicians to Jupiter, the astronomical symbol for whom is ♃. When the Latin form is used, the expression "take thou" requires the use of the genitive for the ingredients and the accusative for the amounts of drugs. If the amount of the drug is not designated, the name of the drug is written in the accusative. The necessity for proper case endings when using the Latin form leads the physician either to numerous errors or to the use of abbreviations to avoid the issue.

Inscription. The inscription is the body of the prescription and contains the name and amount of each ingredient. Drugs are written for by official names or official abbreviations. The use of official abbreviations is permissible; but when a possibility of error exists, names of drugs should be written out. For example, "sulf." may be mistaken for sulfide or sulfonate, and "chlor." may be mistaken for chlorate or chloral. The name of each drug is placed on a separate line directly under the preceding one. The names of the drugs are capitalized. The order of the ingredients, should there be more than one, is as follows:

> *Basis.* The basis is the principal drug and gives the prescription its chief action.
> *Adjuvant.* As the name suggests, the adjuvant is a drug which aids or increases the action of the principal ingredient.
> *Corrective.* The corrective modifies or corrects undesirable effects of the basis or adjuvant.
> *Vehicle.* The vehicle is the agent used as a solvent for the solution, to increase the bulk, or to dilute the mixture.

This order is routinely used in prescribing drug mixtures. An exception occasionally occurs when the adjuvant or corrective is a highly potent drug, under which circumstance it may be placed first. An example of this is the prescribing of small amounts of codeine in an analgesic mixture with salicylate; codeine, though given as an adjuvant, may be placed first. Many prescriptions containing only one or two drugs obviously do not have adjuvants, correctives or vehicles.

Subscription. The subscription contains the directions to the pharmacist. Formerly, directions were quite elaborate and often covered an entire page. Today, the pharmacist is much better trained in the compounding of prescriptions than physicians can hope or desire to be, and therefore he is allowed to use his own judgment in the employment of his art. The directions usually consist of a short sentence such as, "Make a solution," "Divide into 10 pills," "Mix and place into 10 capsules," etc.; or it is only a word such as "Mix." The latter is commonly written as the letter "M," from the Latin "misce" (mix), which the druggist proceeds to do according to his art. The abbreviation "M" also is written as M̶ and M̶s. The same language (English or Latin) is used in the subscription as in the inscription.

Signature. The signature of the prescription consists of the directions to the patient. The term signature does not refer to the physician's name, but is derived from the Latin "signa," meaning write, mark or label. In English, directions are prefixed with the word

"Label"; in Latin, by the word "Signa," or the abbreviations "Sig." or "S." Occasionally, this part of the prescription is called the "transcription," and the term signature is then reserved for the physician's name.

The directions to the patient should be written in English regardless of the language used in the remainder of the prescription. The average physician, however, frequently inserts Latin abbreviations into the directions, and although this is not the best form it may be excusable as a time saver. One may, for example, write ʒj t.i.d.p.c., which the pharmacist translates into English as "one teaspoonful three times daily after meals." Regardless of the symbols, abbreviations or language used by the physician, the pharmacist *always* writes the label in English.

The directions contain instructions as to the amount of drug to be taken, the time and frequency of the dose, and other factors such as dilution, route of administration, etc. If the drug is to be used externally only, or to be shaken well before using, or if it is a poison, such facts are included. The pharmacist has printed labels, covering many of these points, which he attaches to the bottle, and often he affixes them at his own discretion. Directions should be clear but brief, and should occupy no more space than is available in the label to be placed on the container.

The expression "take as directed" should be avoided. An ill patient or a distracted and worried parent or relative cannot always be relied upon to remember clearly the verbal directions given by the physician, or he may remember them incorrectly. If the directions are too lengthy or complicated to be placed in the prescription, they may be written on a separate instruction sheet and left with the patient. Directions which would be embarrassing to the patient if placed on the prescription should be given in private.

Often it is desirable to prevent the patient from having the prescription refilled. This is especially true when prescribing drugs such as barbiturates, arsenic and bromide, the continued use of which may lead to toxic effects from cumulative action. The abbreviation "Non. rep." (non repetatur: do not repeat) is the instruction to the druggist that the prescription is not to be refilled. This restriction may also prevent a well-meaning but none too wise patient from passing on the prescription to a friend who may be suffering from superficially similar symptoms. The abbreviation Non. rep. need not be written on narcotic prescriptions, which by law cannot be refilled. The abbreviation "Pp." (pauperisimus: pauper) placed on the prescription means that the physician is receiving little or no compensation for his services and that the dispenser likewise should charge as little as possible. The letters "Q.R." (quantitum rectum: correct amount) are occasionally placed on a prescription if the dose prescribed is unusual. It notifies the pharmacist that a mistake has not been made, and saves time otherwise lost in verifying the physician's dosage. The practice of using exclamation points to call attention to an unusual amount of drug sometimes leads to error in the apothecaries' system where the exclamation points may be mistaken for numerals.

Finally the physician attaches his signature to the prescription, with the traditional "M.D." following it. If the order is for a narcotic, he must include his U. S. registry number and his complete address.

Classes of Prescriptions. Prescriptions may be divided into two large classes, *non-official* and *official*. A non-official prescription, also called magistral or extemporaneous, is the type in which the physician selects the drugs and doses which he desires. The official prescription is one which calls for a drug or mixture by name, the recipe for which is given in the U.S.P. or N.F. Examples of these two types may now be given and will serve to elucidate the principles of prescription writing.

Non-official Prescriptions. A typical extemporaneous prescription illustrating the four classical divisions enumerated is as follows:

(No. 3)

John Smith, Feb. 5, 1940.
596 Main St.,
New Haven, Conn.

℞

Ephedrine Sulfate	0|4
Sodium Iodide	15|0
Sodium Bromide	20|0
Syrup of Glycyrrhiza, to make	200|0

M.

Label: One teaspoonful with a glass of water three times daily.

In this prescription, given to a patient with chronic bronchial asthma, the ephedrine sulfate is the basis, the sodium iodide the adjuvant, the sodium bromide the corrective to counteract the central stimulant action of the ephedrine, and syrup of glycyrrhiza the vehicle.

When drugs are to be taken internally, exact dosages are required. It is therefore necessary in writing a prescription to know the single dose of each ingredient, the number of doses to be taken each day, and the number of days of medication. These data allow the calculation of the total dosage of each ingredient in the prescription. Suppose it is desired to prescribe an anodyne-expectorant cough mixture to be taken orally every four hours for an unproductive, exhausting cough. This means that at least four doses will be taken daily. If teaspoonful doses (five cc) are used and enough medicine is dispensed to last five days, there will be needed approximately 20 doses or a 100 cc total volume. If the mixture is to contain codeine phosphate (anodyne), ammonium chloride (expectorant) and elixir of terpin hydrate (vehicle), the calculation and construction of the prescription may be shown as follows:

(No. 4)

Tom Brown, Feb. 21, 1940.
43 Englewood Drive,
New Haven, Conn.
℞

<table>
<tr><th></th><th></th><th></th><th>Single dose</th><th>x</th><th>No. of doses</th></tr>
<tr><td>Codeine Phosphate</td><td>0|20</td><td>←→</td><td>10 mgm</td><td>x</td><td>20</td></tr>
<tr><td>Ammonium Chloride</td><td>10|0</td><td>←→</td><td>0.5 gram</td><td>x</td><td>20</td></tr>
<tr><td>Elixir of Terpin Hydrate, to make</td><td>100|0</td><td>←→</td><td>5.0 cc</td><td>x</td><td>20</td></tr>
</table>

M.

Label: One teaspoonful in a tumbler of water *for cough* every four hours, if necessary.

John Doe, M.D.
U.S. Reg. No. 931

The principles of calculation of dosage illustrated apply also to prescriptions for dry forms of medication to be taken internally. Whereas it is fairly easy to ingest liquid medicines, it may be difficult to swallow pills, tablets or capsules which are too large. Therefore these are limited to approximately 0.5 gram in bulk (for adults) for most medicines. If a larger amount is required for the single dose, the drug must be divided into two or more tablets or capsules for each dose. If the ingredients make too small a bulk to be dispensed conveniently in solid form, an inert powder may be added. There are many such powders and excipients (talc, licorice, lactose, gentian, etc.), and the pharmacist often selects and adds them at his own discretion.

Suppose that it is desired to prescribe in capsules an analgesic mixture containing acetylsalicylic acid, acetophenetidin, and barbital for a patient with painful myositis. The medicine is to be taken every four hours (*i.e.*, four doses per day) and enough prescribed to last five days. The construction of the prescription is as follows:

(No. 5)

Mary Thomas, July 29, 1939
606 Constitution Ave.,
New Haven, Conn.
℞

<table>
<tr><th></th><th></th><th></th><th>Single dose</th><th>x</th><th>No. of doses</th></tr>
<tr><td>Acetylsalicylic Acid</td><td>6|0</td><td>←→</td><td>0.3 gram</td><td>x</td><td>20</td></tr>
<tr><td>Acetophenetidin</td><td>6|0</td><td>←→</td><td>0.3 gram</td><td>x</td><td>20</td></tr>
<tr><td>Barbital</td><td>2|0</td><td>←→</td><td>0.1 gram</td><td>x</td><td>20</td></tr>
</table>

Mix and divide into 40 capsules

Label: Take two capsules every four hours for pain, if necessary.

Prescriptions for medicines to be taken internally may also be written by the single dose method. The pharmacist is then instructed to prepare a given number of doses and himself must carry out the calculations illustrated above. For example, prescription No. 5 if written by the single dose method would appear as follows:

(No. 6)

℞

Acetylsalicylic Acid	0	3
Acetophenetidin	0	3
Barbital	0	1

Make 20 such doses and place in 40 capsules.

Label: Take two capsules every four hours for pain, if necessary.

Although in a strict sense this technic is permissible, it is a lazy man's way of shifting the burden to the pharmacist and is not considered the best form. It is best for the physician to do the calculating rather than depend on a clerk of unknown ability. Under certain circumstances, however, the single dose method is preferable. This applies especially to the prescribing of tablets of potent alkaloids, such as scopolamine, morphine, atropine, etc., which are supplied to the pharmacist by manufacturing drug houses in prepared tablets of fixed drug content. Examples of such orders are as follows:

(No. 7)

℞

Atropine Sulfate	0	0005
Tablets No. 20		

Label: Take one tablet three times daily before meals.

(No. 8)

℞

Morphine Sulfate	0	015
Hypodermic tablets No. 20 (Original vial)		

Label: One tablet by hypodermic injection for pain every four hours, if necessary.

The prescription for morphine requires the physician's narcotic registry number and the directions for hypodermic administration are given to the nurse or attendant. The patient is rarely allowed to administer morphine parenterally to himself.

Prescriptions for ointments are usually fairly simple to construct because the ingredients may be calculated on a *percentage basis* rather than by absolute doses. Suppose that it is desired to prescribe an ointment for a fungus infection of the feet, and salicylic acid (three per cent) and benzoic acid (six per cent) are to be incorporated in a base of lanolin and white petrolatum. If 50 grams of ointment are to be dispensed, the order appears as follows:

(No. 9)

℞

Salicylic acid	1	5
Benzoic acid	3	0
Lanolin, White Petrolatum, to make	50	0

Make an ointment

Label: Apply a thin film to the affected parts night and morning.

It will be noted that exact proportions of lanolin and white petrolatum are not given. This allows the druggist to use his own judgment concerning the relative amounts of lanolin and petrolatum to be incorporated in the ointment. If equal parts of these bases are desired they are prescribed as follows:

℞

Lanolin, Petrolatum, of each an equal amount to make	50	0

The aforementioned ointment is essentially one-half strength Whitfield's Ointment, N.F.

When prescribing locally acting drugs, the *percentage form may be used as such* rather than as a basis for calculating absolute amounts of ingredients. Prescription No. 9 thus may be written as follows:

(No. 10)

℞
Salicylic acid 3%
Benzoic acid 6%
Lanolin,
White Petrolatum,
to make 50|0
M.
Label: etc.

Likewise liquid preparations for local administration, such as nasal sprays, inhalants gargles, liniments, lotions, douches and enemata, may be similarly ordered. For example, a nasal spray of one per cent ephedrine may be prescribed as follows:

(No. 11)

℞
Ephedrine 1%
Light Liquid
Petrolatum,
to make 30|0
M.
Label: Use as a nasal spray with atomizer, as necessary.

One may desire to prescribe an ointment of 10 per cent sulfur. The U.S.P. includes an official Sulfur Ointment which contains 15 per cent precipitated sulfur in wool fat (five per cent), yellow wax (five per cent) and white petrolatum (75 per cent). This prescription may be written as follows:

(No. 12)

℞
Sulfur Ointment 10% 50|0
Label: Apply twice daily to affected skin.

Although this prescription does not call for the U.S.P. percentage of sulfur, the use of the official title indicates to the pharmacist that the physician wishes the U.S.P. preparation diluted to a 10 per cent sulfur content.

A prescription for a lotion for external use on the skin is similar in construction to that for an ointment in that only the approximate percentages of the ingredients and not absolute doses need be ordered. A prescription for a simple lotion incorporating eight per cent prepared calamine (essentially a pink insoluble powder of zinc oxide), eight per cent zinc oxide and two per cent glycerin in lime water is written as follows:

(No. 13)

℞
Prepared Calamine 16|0
Zinc Oxide 16|0
Glycerin 4|0
Solution of Calcium Hydroxide,
to make 200|0
M.
Label: Shake well and apply to sunburned areas as needed.

This lotion is identical with the N.F. Calamine Lotion. It is often modified to suit the specific needs of the patient. Many expensive proprietary lotions have essentially the same composition. A pleasant odor can be obtained by the addition of 15 or 20 per cent rose water. If the skin lesion itches, phenol may be added to the lotion in one or two per cent concentration. Occasionally, olive oil is incorporated to the extent of 30 per cent, if an emulsion rather than a lotion is desired.

Inhalant mixtures follow the same general form as for ointments and lotions, it being necessary only to know the approximate percentage strength of each ingredient.

This principle holds true for most medicines applied to surfaces of the body. Suppose that it is desired to prescribe a mixture of volatile oils and balsams to be used as a medicated steam inhalation in chronic bronchitis. The prescription can be written as follows:

(No. 14)

℞

Eucalyptol	15	0
Creosote	5	0
Pine Tar	5	0
Menthol	1	5
Compound Tincture of Benzoin, to make	100	0

M.

Label: Put a teaspoonful in boiling water and inhale steam as directed.

The important point to remember in all mixtures of locally acting medicaments is the percentage beyond which it is unwise to go. In the foregoing prescription, for example, the creosote is the most irritating substance and a concentration of more than five per cent should not be used.

Often a prescription may contain only one active ingredient and yet several agents may be required to make the drug palatable. Suppose that a child five years of age with a tapeworm infestation is to be given oleoresin of aspidium. The drug is a greenish oily liquid with an offensive taste hard to disguise. The dose is important because the drug is quite toxic. For children, 0.5 gram is given for each year of age up to a total dose of five grams. The details of treatment are fairly intricate and therefore specific instructions are left with the patient's mother rather than put on the label. A prescription for a liquid preparation may be written as follows:

(No. 15)

Master John Brown, Age 5, Aug. 27, 1939.
374 Crystal Boulevard,
New Haven, Conn.

℞

Oleoresin of Aspidium	2	5
Powdered Acacia	8	0
Syrup of Ginger	10	0
Peppermint Water, to make	60	0

M.

Label: To be taken in two doses, one-half at 8 A.M. and the remainder at 9 A.M. as per written directions. Shake well before using.

The acacia allows the water-insoluble oleoresin to stay in suspension and renders it less disagreeable to the taste. The syrup of ginger is a corrective flavoring agent, and the peppermint water is the vehicle. One may omit the dose of acacia and allow the druggist to use the amount he deems necessary. It is then written as follows: "Powdered Acacia, sufficient amount ------." If the oleoresin of aspidium is to be given to an adult, the drug may be more conveniently prescribed in sealed gelatin capsules, as follows:

(No. 16)

℞

Oleoresin of Aspidium	5	0

Divide and place in 10 hard gelatin capsules and seal.

Label: Take 5 capsules at 8 A.M. and 5 capsules at 9 A.M. Follow written directions.

Summary. It is now possible to summarize the steps taken in the construction of the average extemporaneous prescription.

(1) The superscription including the name and address of the patient, the date, and the symbol ℞ are written first.

(2) The best remedy for the patient's illness is then ordered by its official name, followed by any additional drugs which are necessary to aid, modify or correct the action of the main ingredient.

(3) Depending on the form in which the medicine is to be given (solution, powder, capsule, etc.), the proper vehicles, flavors or excipients are then recorded.

(4) The directions to the patient are now written. This determines the size of the dose, the number of doses per day and occasionally the duration of medication. The total number of doses and the total bulk of the prescription can then be readily calculated.

(5) The correct total amounts for each drug may now be filled in because the single dose of each is known and need only be multiplied by the total number of doses.

(6) The directions to the pharmacist are now written. The prescription should be examined for incompatibilities, reread and signed.

Official Prescriptions. Official prescriptions in the United States are those which order recipes included in the U.S.P. or N.F. They are prescribed by their official names and the specific ingredients need not be listed. Examples illustrating official prescriptions may now be given. A survey of the U.S.P. and N.F. will acquaint the physician with the wide scope and value of the official preparations.

(No. 17)

℞
Alkaline Aromatic Solution (N.F.) 250|0

Label: Use freely as a mouth wash, diluted with equal parts of water.

It is not absolutely necessary to include the letters N.F. in parentheses, but this aids in calling the pharmacist's attention to the official nature of the solution, especially if it is rather uncommon or if there is possibility of confusion. In prescribing official preparations, one need give no directions regarding its compounding, because these are specified in the U.S.P. or N.F., and the pharmacist is obliged to follow them implicitly. The advantages of using official prescriptions are clear when one considers that Alkaline Aromatic Solution, N.F., contains potassium bicarbonate, sodium borate, thymol, eucalyptol, methyl salicylate, tincture of cudbear, alcohol, glycerin and water. If the physician wanted to write an extemporaneous prescription of the same general type, he might find the task difficult. Likewise, the pharmacist's fee would be greater, because the more common official preparations are dispensed by drug houses and kept in stock.

Suppose that it is desired to prescribe arsenic for a patient with chronic myelogenous leukemia. An official U.S.P. preparation may be ordered by title as follows:

(No. 18)

℞
Solution of Potassium Arsenite 20|0
Non. rep.
Supply a U.S.P. standard medicine dropper.

Label: Take 6 drops three times daily for two days. Then increase the dose by one drop every other day until a dose of 12 drops is reached.

This prescription may also be ordered as "Fowler's Solution." The abbreviation Non. rep. prevents the refilling of the medicine, and is used because of the possibility of poisoning from too prolonged use of an arsenical. The dose is given in "drops" instead of minims because a standard U.S.P. medicine dropper is ordered and this delivers 20 drops per cc. The directions to the patient conform to the arsenical dosage discussed on page 745, and the 20 cc total amount as a rule does not allow the possibility of toxic effects.

The extemporaneous prescription No. 4 for a codeine-containing cough mixture may be ordered by an official prescription containing similar ingredients (except for ammonium chloride) provided the physician is willing to accept the fixed drug content which official preparations necessitate. The N.F. contains a cough medicine incorporating codeine (two mgm per cc; 10 mgm per teaspoon dose) in the vehicle Elixir of Terpin Hydrate. This prescription may be ordered by its official title as follows:

(No. 19)

℞
Elixir of Terpin Hydrate
and Codeine, N.F. 100|0

Label: One teaspoonful in water every four hours for cough, if necessary.

The concentration of codeine in this elixir is less than that which requires a physician's narcotic prescription order.

The extemporaneous prescriptions cited (Nos. 9 and 10) for an ointment of salicylic and benzoic acids may be ordered by the official title provided the physician desires the concentrations fixed by the N.F. The Compound Ointment of Benzoic Acid, N. F. (Whitfield's Ointment) contains benzoic acid (12 per cent) and salicylic acid (six per cent) in wool fat (five per cent) and white petrolatum. It is ordered as follows:

(No. 20)

℞
Compound Ointment of Benzoic Acid (N.F.) 30|0
Label: Apply a thin film to affected parts night and morning.

The non-official prescription (No. 13) for a lotion of calamine and zinc oxide in glycerin and lime water is identical with Calamine Lotion, N.F., and may be ordered by the official title as follows:

(No. 21)

℞
Calamine Lotion, N.F. 200|0
Label: Apply freely to affected parts several times daily.

As a final example of the use of official prescriptions for complicated drug mixtures the familiar preparation, paregoric, may be cited. This can be ordered as Paregoric or as Camphorated Tincture of Opium (U.S.P.), as follows:

(No. 22)

℞
Camphorated Tincture of Opium, U.S.P. 100|0
Label: One teaspoonful three times daily after meals.

A narcotic order is not required for this prescription because the amount of opium (four mgm per cc) is within the exemption limit. If the ingredients in paregoric were to be ordered extemporaneously, one would have to write a prescription containing tincture of opium (four cc), oil of anise (0.4 cc), benzoic acid (0.4 gram) and camphor (0.4 gram) in sufficient diluted alcohol and glycerin to make 100 cc.

Dosage. Dosage is extremely important in prescription writing. One must know the method of calculating doses and the factors influencing the amount of drug to be prescribed. It is also essential that the interconversion of the metric and apothecaries' systems be quickly and accurately handled.

Factors Influencing Doses of Drugs. Many factors influence the doses of drugs. These include the age, weight, sex of the patient, the nature of the illness, the absorption, fate and excretion of the drug, and also factors of idiosyncrasy, tolerance, habituation and addiction. These points are fully discussed elsewhere (page 11).

Calculation of Dosage. Calculation of dosage in the metric system is easily accomplished and the technic has been outlined especially in connection with prescriptions No. 4 and No. 5. The same principles hold true for the apothecaries' system, but the calculation is impeded by the cumbersome arithmetical values of the units employed. Many devices for facilitating calculation in the apothecaries' system have therefore been advanced but as a rule these are more difficult to employ than the direct method of multiplication.

Factors Influencing the Total Bulk of the Prescription. The number of days for which medication is contemplated, the number of doses per day, and the size of each dose determine the bulk of the prescription. Certain other factors, however, are of lesser but distinct importance. The stability of the drug may determine the amount ordered. The cost of the drug must also be considered. Likewise, the necessity for alteration in treatment or changes in the relative doses of the several ingredients in a mixture are factors to be taken into account. The size of standard bottles is also a factor. If a total volume of 100 cc is ordered and the druggist has only apothecaries' sizes the medicine will be placed in a ℥iv (120 cc) bottle. Some patients resent paying for a partially filled bottle of medicine. Fortunately, metric bottles are coming into wider use.

Accuracy of Dosage. Extreme accuracy of dosage is unnecessary except for very potent drugs that are given in amounts of a few milligrams or less, and it is absurd when prescribing relatively non-toxic drugs which can be given in a single dose of one-half gram or more. Therefore, in calculating the total amount of a drug to be ordered in a prescription, a "rounding off" process is employed. For example, 0.52 gram may be taken as 0.50 gram; 0.68 gram as 0.70 gram; ʒi̅i̅j̅ gr.v̅ is taken as ʒi̅i̅j̅; and ʒi̅i̅j̅ gr. lv is rounded off to ʒiv. In general, a variation of not more than 10 per cent in dosage is permissible. Accuracy in dispensing small amounts of toxic drugs is not obtained with the pharmacist's balance but by the use of ready-made pills and tablets supplied by manufacturing drug houses.

Official Doses. Official doses in the United States are those given in the U.S.P. and N.F. and represent average amounts usually prescribed as single doses to adults. Official doses are often greatly exceeded depending upon the requirements of the patient's illness, but they serve as accepted standards and are also of value in indicating the relative activity of drugs.

Latin Phrases and Abbreviations. There are a number of Latin phrases and abbreviations which should be known. Some of these are a traditional part of prescription writing and are often employed especially in the directions to the pharmacist or patient, even though the remainder of the prescription is written in English. The pharmacist then translates the directions to the patient into English. The more common phrases and abbreviations are as follows:

ad libitum (ad lib.)	at pleasure; freely; as much as wanted
ana (aa or a̅a̅)	of each
ante (ā)	before
ante cibum (a.c.)	before meals
aqua	water
aqua destillata	distilled water
bis in die (b.i.d.)	twice daily
capsula (cap.)	capsule
chartula	powder
cum (c̄)	with
dividatur in partes aequales (d. in p. aeq.)	let it be divided into equal parts
fac; fiat; fiant (f; ft.)	make; let be made; let them be made
fac tales doses No. XX	make twenty such doses
gutta; guttae (gtt.)	a drop; drops
hora (h.)	hour
misce (M.)	mix
misce et divide in	mix and divide into
misce et fac solutionem	mix and make a solution
misce et pone in	mix and place into
misce et tere bene	mix and stir well
non repetatur (non rep.)	do not repeat
numerus (No.)	number
pauperisimus (Pp.)	pauper
pilula (pil.)	a pill
post (p̄)	after
post cibum (p.c.)	after meals
pro re nata (p.r.n.)	according to circumstances; occasionally
quantum satis, sufficit, or sufficiat (q.s.)	a sufficient amount; as much as is necessary
(q.s.ad)	a sufficient amount to make
quaque die (q.d.)	every day
quaque hora (q.h.)	every hour
(q. 4 h.)	every four hours
quater in die (q.i.d.)	four times a day
secundem artem (S.a.)	according to the practice
semis (ss or s̅s̅)	one-half
sine (s̄)	without
si opus sit (s.o.s.)	if necessary
ter in die (t.i.d.)	three times a day
tritura et fac tabellas	triturate and make tablets

Vehicles, Flavors and Coloring Agents. This subject is mainly concerned with drugs taken orally, especially liquid preparations. Oral medication should be encapsulated whenever possible, but there are instances when liquids or powders are necessary. It is therefore essential to know how to made medicines sufficiently palatable so that they will be taken. Disagreeable substances often tempt the patient not to take his drug as ordered, and if the medicine is too obnoxious it may inhibit absorption or cause nausea and vomiting. Children often cannot be induced to take a second dose of a repulsive drug. It is unpardonable to insult a sick child's palate. Even cod liver oil can be made fairly palatable as in the *Emulsion of Cod Liver Oil,* U.S.P. Patients no longer expect medicines to taste bitter, and many patented nostrums flourish only by virtue of their agreeable taste, appealing color or alcohol content. It is certainly wise not only for the physician to be acquainted with the form, color and taste of the drugs he prescribes, but also to consult the patient as to his taste or preference in the matter. It would be foolish, for example, to prescribe a drug in *Syrup of Cocoa* for a patient who detests chocolate or is allergic to it.

Watery Vehicles. Watery vehicles include the aromatic waters, the syrups and the mucilages.

1. Aromatic Waters. Aromatic waters are used as vehicles for water-soluble substances and salts, but cannot mask the taste of very disagreeable drugs. Some of the more common flavored waters are as follows:

Anise Water (U.S.P.)
Bitter Almond Water (U.S.P.)
Camphor Water (U.S.P., B.P.)
Cinnamon Water (U.S.P., B.P.)
Fennel Water (U.S.P.)
Peppermint Water (U.S.P., B.P.)
Spearmint Water (U.S.P.)
Wintergreen Water (N.F.)

2. Syrups. The syrups are useful as vehicles for water-soluble drugs and act both as solvents and flavoring agents. Simple syrup contains 85% of sucrose in water. The flavored syrups usually consist of simple syrup diluted with appropriate flavoring substances. Some of the more common syrups are as follows:

Syrup (Simple Syrup), U.S.P., B.P.
Syrup of Acacia, N.F.
Syrup of Cinnamon, N.F.
Syrup of Cherry, N.F.
Syrup of Citric Acid, U.S.P.
Syrup of Cocoa, N.F. V.
Syrup of Ginger, N.F., B.P.
Syrup of Glycyrrhiza (Licorice), N.F.
Syrup of Orange, U.S.P., B.P.
Syrup of Orange Flowers, U.S.P.
Syrup of Prepared Cacao, N.F.
Syrup of Raspberry, N.F.
Syrup of Rhubarb, N.F.
Syrup of Tolu Balsam, U.S.P., B.P.
Syrup of Wild Cherry, U.S.P., B.P.
Aromatic Syrup of Eriodictyon, N.F.
Aromatic Syrup of Rhubarb, U.S.P.
Compound Syrup of Sarsaparilla, U.S.P

Some of these syrups deserve special mention. Syrups of citric acid and orange cannot be used with alkaline carbonates because they contain free citric acid. The syrup of cherry is a true fruit syrup and is more pleasant than the syrup of wild cherry which comes from wild cherry bark and has an unpleasant astringent taste. The *Syrup of Cinnamon (N.F. VI)* is an excellent vehicle for sodium salicylate, iron and ammonium citrate, and ammonium chloride.

(No. 23)

℞

Iron and Ammonium Citrate	30	0
Water	30	0
Syrup of Cinnamon (N.F. VI), to make	120	0

M.

Label: One teaspoonful in water taken through a glass straw, three times daily after meals.

Syrup of Licorice (glycyrrhiza) is an excellent vehicle for saline substances because of its colloidal properties and its double sweetness due to the sugar and the lingering taste of the licorice.

(No. 24)

℞

Sodium Bromide	30	0
Anise Water	30	0
Syrup of Licorice, to make	120	0

M.

Label: One teaspoonful with water after meals and at bedtime.

Syrup of Acacia due to its colloidal nature is especially valuable in disguising substances with burning tastes, such as urea.

(No. 25)

℞

Urea	60	0
Syrup of Acacia, to make	120	0

M.

Label: Tablespoonful in water every 3 hours.

Fruit syrups, such as *Syrup of Raspberry,* are especially effective for masking sour tastes.

(No. 26)

℞

Diluted Hydrochloric Acid	60	0
Syrup of Raspberry, to make	240	0

M.

Label: Take two teaspoonfuls in a glass of water during meals. Sip through a straw.

The *Aromatic Syrup of Eriodictyon* (yerba santa) has been called by Fantus a "therapeutic masterpiece." It disguises the bitterness of alkaloids by virtue of a resinous substance with which the alkaloids combine. There is sufficient alkali in the syrup to keep the combination in solution. Bitter alkaloids, such as quinine, codeine, etc. are especially well masked.

(No. 27)

℞

Quinine Bisulfate	5	0
Aromatic Syrup of Eriodictyon, to make	60	0

M.

Label: One teaspoonful every 4 hours with water.

Quinine is so bitter that it has been remarked that "the best syrup for quinine is a gelatin capsule."

In a study of the comparative efficiency of the commonly used flavoring agents by actual trial on more than 600 individuals, Wright (1937) found many interesting facts. These are depicted in Tables 64, 65, 66, and 67, a study of which will enable one to select the best agents available as vehicles and flavors for a variety of purposes.

3. Mucilages. The mucilages are also suitable as vehicles for water-soluble substances, and are especially useful for suspensions and emulsions. The two most commonly used are acacia and tragacanth.

Acacia. Acacia (*Gum Arabic*), U.S.P., B.P., is the dried gummy exudation from the stems and branches of an African shrub, *Acacia senegal.* The *Mucilage of Acacia* (*U.S.P.*) is a 35 per cent solution of acacia in distilled water with 0.1 per cent sodium benzoate added as a preservative. Acacia is precipitated by strong alcohol. A 10 to 15 per cent concentration of acacia is usually sufficient to hold insoluble or immiscible substances in a state of suspension or emulsion. The mechanism of masking of taste by acacia is that the dispersed phase is surrounded by a thin film of the colloidal acacia solution. Acacia is further discussed on page 766.

Tragacanth. Tragacanth, in contrast to acacia, is not precipitated by alcoholic preparations. The *Mucilage of Tragacanth* (*U.S.P.*) is a six per cent concentration in glycerin (18 per cent) and water. *Tragacanth,* U.S.P., B.P., is the dried gummy exudation from an Asiatic herb, *Astragalus gummifer.*

Hydroalcoholic Vehicles. Hydroalcoholic vehicles are suitable for drugs soluble either in water or dilute alcohol. The most important hydroalcoholic vehicles are the *Elixirs.* These solutions contain approximately 25 per cent alcohol. There are many official medicated elixirs containing specific drugs, such as Elixir of Sodium Bromide, N.F., Elixir of Iron, Quinine and Strychnine, N.F., Elixir of Sodium Salicylate, N.F., Elixir of Phenobarbital, N.F., and about two score more. The common, non-medicated elixirs used purely as vehicles and diluents are as follows:

Aromatic Elixir, U.S.P. This is also known as *Simple Elixir.* It consists essentially of compound spirit of orange in syrup, alcohol and water. It is a useful vehicle for a wide range of purposes.

Red Aromatic Elixir, N.F. This elixir differs from aromatic elixir only in its red color, obtained by the addition of tincture of cudbear. It is used in the same manner as *Aromatic Elixir.*

Table 64

ORDER OF PREFERENCE OF FLAVORING AGENTS ALONE AND WITH THE ADDITION OF AN ALKALOID

Preference for Flavor Alone		Efficiency in Disguising Bitter Taste †	
Flavoring Agent	* Score %	Flavoring Agent	* Score %
Syrup of Cocoa, N.F. V	91	Syrup of Cocoa, N.F. V	81
Syrup of Prepared Cacao, N.F. VI	88	Syrup of Raspberry, N.F. V	77
Syrup of Raspberry, N.F. VI	71	Aromatic Syrup of Eriodictyon	73
Syrup of Orange	53	Syrup of Prepared Cacao, N.F. VI	67
Syrup of Cherry, N.F. VI	51	Syrup of Cherry, N.F. VI	48
Compound Syrup of Sarsaparilla	48	Syrup of Cinnamon	41
Syrup of Citric Acid	46	Compound Syrup of Sarsaparilla	39
Aromatic Syrup of Eriodictyon	35	Syrup of Citric Acid	35
Elixir of Licorice	33	Elixir of Licorice	27
Syrup of Cinnamon	32	Aromatic Elixir	27
Syrup of Wild Cherry	29	Syrup of Orange	21
Aromatic Elixir	27	Syrup of Wild Cherry	14
Syrup of Licorice	26	Syrup of Licorice	12

Wright, 1937.

* Score: Results were tabulated and scored on basis of 3 points for first choice, 2 for second choice, 1 for third choice, and no credit for fourth choice. These ratings were then expressed as a percentage of a perfect first choice. Thus a score of 75% or more may be considered highly effective, a score of from 50% to 65% indicates a second grade flavoring agent, a score of from 35% to 50% denotes a third grade flavoring agent, and a score of less than 35% represents a practically worthless agent. The scoring also applies to the subsequent tables.

† 0.1% of quinine bisulfate was added to the various flavoring agents. This equals in intensity the bitterness produced by 30 mgm of codeine sulfate to the teaspoonful (5 cc).

Table 65

ORDER OF PREFERENCE OF FLAVORING AGENTS IN DISGUISING (A) AMMONIUM CHLORIDE AND (B) TINCTURE OF DIGITALIS

(A) Efficiency in Disguising Ammonium Chloride *		(B) Efficiency in Disguising Tincture of Digitalis †	
Flavoring Agent	** Score %	Flavoring Agent	Score %
Syrup of Cinnamon	64	Syrup of Raspberry, N.F. VI	83
Syrup of Orange	61	Syrup of Prepared Cacao, N.F. VI	77
Compound Syrup of Sarsaparilla	58	Aromatic Syrup of Eriodictyon	73
Aromatic Syrup of Eriodictyon	54	Syrup of Cherry, N.F. VI	60
Syrup of Citric Acid	50	Syrup of Citric Acid	60
Syrup of Cherry, N.F. VI	47	Tincture of Vanillin 20 per cent in Syrup	59
Syrup of Cocoa, N.F. V	42	Syrup of Orange	57
Syrup of Wild Cherry	41	Syrup of Wild Cherry	54
Syrup of Raspberry, N.F. VI	40	Aromatic Elixir	32
Elixir of Licorice	35	Iso-Alcoholic Elixir (high)	24
Syrup of Prepared Cacao, N.F. VI	34	Iso-Alcoholic Elixir (50–50)	24
Aromatic Elixir	23	Iso-Alcoholic Elixir (low)	14
Syrup of Licorice	11	Tincture of Vanillin 10 per cent in Syrup	10

Wright, 1937.

** For scoring, see Table 64.

* 0.4 Gm. of ammonium chloride per teaspoonful (5 cc).

† 0.5 cc of tincture of digitalis per teaspoonful (5 cc).

Table 66

COMPARATIVE EFFICIENCY OF FLAVORING AGENTS IN DISGUISING AMMONIUM CHLORIDE AND SODIUM BROMIDE

Flavoring Agent	Percentage Efficiency in Disguising 8% Ammonium Chloride	 17.5% Sodium Bromide*
Syrup of Cinnamon	64	66
Syrup of Orange	61	64
Compound Syrup of Sarsaparilla	58	52
Aromatic Syrup of Eriodictyon	54	47
Aromatic Elixir	23	..
Elixir of Sodium Bromide	..	23

Wright, 1937. For scoring, see Table 64.

* This equals the concentration of sodium bromide in the official Elixir of Sodium Bromide, N.F., in which Aromatic Elixir is used as the vehicle.

Table 67

ALL-ROUND EFFICIENCY OF THE VARIOUS FLAVORING AGENTS

Flavoring Agent	*Score %	Flavoring Agent	Score %
Syrup of Cocoa, N.F. V	71	Syrup of Orange	48
Syrup of Prepared Cacao, N.F. VI	67	Syrup of Citric Acid	47
Syrup of Raspberry, N.F. VI	68	Syrup of Cinnamon	46
Compound Syrup of Eriodictyon	59	Syrup of Wild Cherry	35
Syrup of Cherry, N.F. VI	52	Elixir of Licorice	32
Compound Syrup of Sarsaparilla	48	Aromatic Elixir	27

Wright, 1937. * For scoring, see Table 64.

Elixir of Glycyrrhiza, U.S.P. This elixir is essentially *Aromatic Elixir* to which has been added 12.5 per cent of fluidextract of glycyrrhiza (licorice). It is helpful for masking bitter and salty substances, but cannot be used for acids or acid salts because the licorice precipitates out.

Iso-alcoholic Elixir, N.F. This elixir is a hydroalcoholic vehicle, with the flavor and taste of *Aromatic Elixir.* Its alcoholic content is adjusted by the pharmacist to meet the requirements of the drugs for which it serves as a vehicle or diluent. For example, if the physician wishes to prescribe a tincture or fluidextract in a vehicle in order to increase the volume and thus make the dose more convenient to measure, it is important that the alcoholic strength of the vehicle be approximately the same as that of the tincture or fluidextract. Otherwise the active principles may be precipitated. A physician need not remember the particular alcoholic strength required but merely prescribes the iso-alcoholic elixir. The pharmacist then consults tables in the N.F. to ascertain how much of the elixirs of low and high alcoholic content to mix in order to obtain the same alcohol concentration as the solution of drug which is being prescribed. Thus, if tincture of digitalis is ordered in iso-alcoholic elixir, the alcohol percentage is adjusted to 70 per cent because this concentration is that of the tincture and the potent glycosides will then not be precipitated out of solution.

(No. 28)

℞

Tincture of Digitalis	10|0
Iso-alcoholic Elixir, to make	60|0

M.

Label: One teaspoonful in water,
morning and evening.

The advantage of diluting the tincture of digitalis with the elixir is that "drops" or minims need not be prescribed, but a teaspoonful dose contains the desired quantity of the tincture.

Alcoholic Vehicles. Alcoholic vehicles are useful for substances soluble in strong alcohols, or as flavors to be added in small quantities to syrups or elixirs. The alcoholic content of these vehicles is in the neighborhood of 50 per cent, twice or more that of the elixirs. There are two types of alcoholic vehicles, the *tinctures* and the *spirits.*

1. Tinctures. Tinctures are alcoholic or hydroalcoholic solutions of the active principles of drugs. They are prepared in a quantitative manner so that a known amount of drug extractives is present. Tinctures of potent drugs are usually made so that the active constituents of 10 grams of the crude drug are contained in 100 cc. Tinctures of less potent drugs contain the extractives of 20 grams of drug per 100 cc. When fresh rather than dried drugs are used, 100 cc of tincture represents 50 grams of drug. Such tinctures as those of iodine, ferric chloride, etc., which contain pure chemicals completely dissolved in the alcoholic vehicle, are exceptions to the accepted definition of a tincture.

Tinctures are *medicated* or *non-medicated. Medicated tinctures* include such well-known preparations as *Tincture of Digitalis,* U.S.P., *Tincture of Belladonna,* U.S.P., *Tincture of Opium,* U.S.P., *Tincture of Nux Vomica,* U.S.P., etc. *Non-medicated tinctures* are used as flavored vehicles or coloring agents. Some of the more common non-medicated tinctures used as coloring agents are the following:

Compound Tincture of Cardamom, U.S.P., B.P. This tincture contains cardamom seed, cinnamon, caraway, cochineal, glycerin and alcohol. It is useful as a coloring agent if added in low percentage either to alcoholic or watery solutions, and is serviceable regardless of the pH of the mixture. A two per cent solution is a pale heliotrope color, and a 10 per cent solution yields a brilliant cherry color.

Tincture of Cudbear, N.F. This tincture is used mainly as a coloring agent in a one-half to two per cent concentration. It is useful either in watery or alcoholic solutions and at all pH's. The tincture has a red indigo color. The *Compound Tincture of Cudbear,* N.F., has caramel added, contains less alcohol, and is used to impart a reddish-brown color. In using coloring agents, it is not necessary to order an exact amount, as illustrated in the following prescription:

(No. 29)

℞

Sodium Bromide	20	0
Tincture of Cudbear, sufficient amount		
Syrup of Orange, to make	100	0

M.

Label: One teaspoonful with meals three times a day.

In filling this order, the pharmacist adds the coloring agent in an amount sufficient to impart a pleasing color to the mixture.

Compound Tincture of Lavender. This coloring agent contains oil of lavender, oil of rosemary, cinnamon, clove, myristica (nutmeg) and red saunders in 70 per cent alcohol. A two per cent concentration imparts a light fawn color, a 10 per cent concentration a brilliant orange. The tincture can be employed with alcoholic and hydroalcoholic preparations and at all pH's. Another tincture useful as a coloring agent is *Tincture of Hydrastis,* N.F. This yields a lemon color at a concentration of one per cent, and a bright yellow color at four per cent.

In addition to the tinctures used as coloring agents, certain aqueous solutions serve the same purpose. Two of these solutions are *Solution of Cochineal,* N.F., and *Solution of Carmine,* N.F. The Solution of Cochineal, which contains a coloring substance derived from an insect, is miscible with alcoholic and watery solutions and is serviceable at neutral, acid and alkaline reactions. In a concentration of 0.2 per cent, it yields a rose color in alkaline or neutral, and a pale pink color in acid solutions. In a concentration of 0.5 per cent, a reddish purple color is obtained in alkaline or neutral, and a dark pink color in acid solutions. Solution of Carmine (also from cochineal) is used as a red coloring agent for watery or alcoholic preparations but cannot be employed if the solution is acid or contains acid-forming salts, due to precipitation of the coloring agent. As little as 0.02 per cent imparts a pale rose hue, and a concentration of 0.2 per cent yields a dark rose color.

Tinctures useful as flavored vehicles are *Tincture of Sweet Orange Peel,* U.S.P., *Tincture of Bitter Orange Peel,* U.S.P., B.P., *Tincture of Lemon,* U.S.P., B.P., *Tincture of Cinnamon,* N.F., *Tincture of Vanilla,* N.F., *Compound Tincture of Gentian,* U.S.P., B.P., and many others.

2. Spirits. Spirits are alcoholic solutions of volatile drugs, usually oils. Spirits used as vehicles contain 10 per cent of the volatile flavoring agent. The commonly used spirits (other than whisky and brandy) are the following: *Spirit of Peppermint,* U.S.P., B.P., *Spirit of Spearmint,* U.S.P., *Spirit of Lavender,* U.S.P., *Spirit of Anise,* U.S.P., *Spirit of Almond,* N.F., and the *Compound Spirit of Orange,* U.S.P.

In addition to spirits used as vehicles for alcoholic solutions, there are medicated spirits such as *Spirit of Nitroglycerin,* U.S.P., *Aromatic Spirit of Ammonia,* U.S.P. and *Sweet Spirit of Nitre,* U.S.P.

Flavoring of Powders. Powders may be flavored with sugars mixed with small amounts of volatile oils. *Oil-Sugar,* N.F., consists of two per cent of a volatile oil mixed with sucrose. The volatile oil may be any of the following: anise, cinnamon, wintergreen, peppermint, etc. These can be ordered as anise oil-sugar, peppermint oil-sugar, etc. *Aromatic Powder,* N.F., is perhaps the most common and pleasant flavoring powder. It contains cinnamon, ginger, cardamom seed and nutmeg. A similar preparation is Aromatic Powder of Chalk, B.P.

Coloring. Many vehicles contain their own distinct color. Coloring agents like the tincture of cudbear may be added to otherwise colorless solutions and may have a distinct psychological effect. Some people still believe that a medicine which looks like water cannot have any virtue. Blue should be avoided as this color is reserved for mercuric chloride solutions. The best way to become acquainted with the colors of vehicles and their variations with dilution and with the reaction of the solution is to enlist a pharmacist's aid in demonstrating them.

Incompatibility. An *incompatibility* exists when the ingredients of a drug mixture interfere with each other in a manner not intended by the physician. Incompatibilities were frequent in the days of "shot-gun" prescriptions containing a large number of substances with varying solubilities and chemical properties. The simpler the prescription, the less chance there is for an incompatibility to occur.

Various types of incompatibilities are recognized. A *chemical* incompatibility exists when two ingredients in a prescription react chemically with each other, as for example, an acid and an alkali. A *physical* incompatibility occurs when liquefaction, deliquescence or precipitation takes place. A *pharmaceutic* incompatibility exists when a prescription becomes unsightly or disagreeable to the taste. A *therapeutic* incompatibility occurs when two drugs which are physiological antagonists are unwittingly prescribed in the same mixture.

The following incompatibilities are those which are likely to be encountered in prescription writing. The list is not complete but contains the points essential for the physician.

Acids. If acids and carbonates are prescribed together, carbon dioxide is liberated from the carbonate. Alkaline salts of organic acids precipitate the salts of heavy metals from aqueous solutions.

Alcohol. Salts of alkaloids are as a rule insoluble in strongly alcoholic solutions. Gums, albumin and many inorganic salts are precipitated by alcohol from watery solutions. Most water-insoluble inorganic drugs are also insoluble in strong alcohol. Alcoholic solutions of water-insoluble drugs should not be prescribed with aqueous liquids.

Alkalis. Acids liberate carbon dioxide from carbonates. Hydroxides and carbonates in aqueous solution with alkaloidal salts cause precipitation of the free alkaloidal bases. Alkalis prescribed with chloral hydrate may produce chloroform. The carbonates of sodium and potassium precipitate salts of heavy metals out of aqueous solution. The bicarbonates of sodium and potassium manifest the same incompatibilities as the carbonates.

Alkaloids. Alkaloids and their salts as a rule should not be prescribed in solution with hydroxides, carbonates, iodides, bromides, iodine, salicylates, benzoates, borates, metallic salts or tannic acid, because precipitation of the alkaloid will occur. If glycerin or alcohol is present in sufficient amount (10 to 50 per cent), however, precipitation is often prevented.

Bromides, Chlorides and Iodides. These are generally soluble in water (except for silver, mercurous, lead and bismuth). High concentrations of bromides and iodides may precipitate alkaloidal salts out of aqueous solution. Iodides oxidize mercurous salts to the toxic mercuric salts, and liberate free iodine in the presence of acid or oxidizing substances.

Chloral Hydrate. This drug forms a liquid if rubbed in a dry state with camphor or menthol. It also reacts with alkalis to produce chloroform. Finally, if dissolved in strong alcohol it may separate out as the oily chloral alcoholate.

Glycosides. Glycosides are incompatible with alkalis, mineral acids and enzymes, because hydrolysis may result.

Gums. Gums are water-soluble and are precipitated by alcohol. Tragacanth, however, is miscible with alcoholic preparations, but a slight flocculent precipitate may form.

Iron. Iron salts should be prescribed alone as a rule. Ferric salts are incompatible with tannic and gallic acids (blue solution or precipitate); with carbolic acid or salicylates (violet color); with hydroxides or carbonates (red iron hydroxide); with acacia solution. Ferrous salts are incompatible with tannic and gallic acids (white precipitate).

Mercury. The salts of mercury show such manifold incompatibilities that they should be prescribed alone unless there is a valid reason for doing otherwise. Mercuric salts are incompatible with alkaloids, glycosides, tannins, proteins, and salts of other metals. Halogen salts of mercury are precipitated by hydroxides.

Oils. Volatile oils in alcoholic solution (*e.g.*, spirits) are thrown out of solution by sufficient dilution with water. Some volatile oils in solution in water (*e.g.*, aromatic waters) may be thrown out of solution by addition of high concentrations of certain soluble inorganic salts. Fixed oils form soaps if prescribed with hydroxides and metal oxides.

Oxidizing Substances. These include especially chlorates, permanganates, peroxides, chromic acid and nitrates. When they are improperly handled or prescribed, there is danger of explosion. Chlorates should not be triturated in a dry state with easily oxidizable substances, and should not be prescribed with glycerin, hydrochloric or sulfuric acid unless considerably diluted with water. Nitric acid should not be employed with easily oxidized substances or with glycerin. If iodine is prescribed with ammonia water to make the so-called colorless tincture of iodine, an explosion may result if sufficient evaporation occurs. Iodine may cause an explosion if mixed with turpentine. Formaldehyde should not be added to oxidizing substances, even if they are in solution.

Resins. Resins are precipitated from alcoholic solutions if sufficient water is added. Soaps are formed if resins are mixed with hydroxides or carbonates.

Salts of Heavy Metals. These salts, as a rule, are incompatible with alkaloids, tannin, proteins, acacia, and a large number of organic substances. They are usually insoluble in alcohol.

Tannates. Tannates are generally insoluble but the amount of tannic acid in galenical preparations rarely causes precipitates except with ferric salts and some alkaloids. Tannic acid may liberate nitric oxide gas from spirit of nitrous ether. Solutions of most galenicals are best prescribed alone.

Water. Most alkaloidal bases are insoluble in water. Most glycosides are also water-insoluble. Resins and neutral and bitter principles are thrown out of alcoholic solution if sufficient water is added. Many water-soluble substances are thrown out of aqueous solution if sufficient alcohol is added.

Certain substances are especially likely to give rise to incompatibilities and should therefore be prescribed alone as a rule. These are as follows:

strong mineral acids
strong alkalis
alkaloids
arsenic
iodides
iron salts
mercury salts
methenamine
permanganates
salicylates
silver salts
tannic acid

Narcotic Regulations. Various Federal and state laws exist to control the standard of purity of drugs and their manufacture, sale and dispensing. These laws must be known and observed by the practitioner. The most important narcotic laws are embodied in the Federal Narcotic Regulations which originated with the Harrison Narcotic Act. The regulations apply to opium and coca leaves and their derivatives and a booklet containing the regulations can be secured for a nominal fee from the government.*

In order to prescribe narcotics, a physician must be registered with the Collector of Internal Revenue, and secure a special tax stamp and registry number. This number must then be indicated on all prescriptions calling for narcotics. A narcotic order must be written in ink or indelible pencil, or typewritten; the name, age and address of the patient must be given, and the date recorded. The purpose for which the narcotic is prescribed must also be designated. Certain ways by which this can be accomplished have been given on page 1309. If the disease is an incurable one like cancer, the phrase "Exception (1), Article 85" may be used instead of the diagnosis; if the narcotic is ordered for an aged or infirm addict whose life would be jeopardized by withdrawal of the drug, the phrase "Exception (2), Article 85" may be employed. The physician must include his address and sign his name in ink or indelible pencil on all prescriptions for narcotics.

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* Narcotic-Internal Revenue Regulations Relating to Importation, Manufacture, Production, Compounding, Sale, Dealing In, Dispensing and Giving Away of Opium or Coca Leaves or Any Compound, Manufacture, Salt, Derivative, or Preparation Thereof. U. S. Government Printing Office, Washington, D. C., 1938. Price, 15 cents.

Narcotics prescribed in small quantities are exempt from the law provided that the medicine does not contain more than any one of the following per fluidounce: two grains (120 mgm) of opium, one-quarter grain (15 mgm) of morphine, one-eighth grain (eight mgm) of heroine (*see* page 207), or one grain (60 mgm) of codeine. These medicines can be prescribed as any other drugs and may be refilled. Narcotic orders, of course, cannot be refilled by the pharmacist and do not require the abbreviation "non rep."

Both the physician and pharmacist are legally responsible for the proper prescribing and dispensing of narcotic drugs. There are many technical details to the narcotic regulations and the physician innocently may violate the law in his professional use of opium derivatives. An adequate and understandable interpretation of the technical language of the narcotic regulations appears in the article by Woodward (1931).

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U.S.P. XII ADDITIONS AND DELETIONS

The U.S.P. XII became official November 1, 1942. A number of important additions and deletions were made, as well as certain changes in policy and scope. An accelerated revision policy was adopted whereby the U.S.P. will be revised every five years, instead of every 10 years, and a "Supplement" issued halfway between. The U.S.P. has always excluded from the list of recognized medicines those of which the composition or mode of manufacture was kept secret; however, the Pharmacopoeia has long accepted some products of recognized therapeutic merit, even when trademarked or manufactured under a process or product patent. In selecting the medicinal substances and preparations for inclusion in the Twelfth Revision, trademark or patent complications which might be involved in some cases have been ignored, the question of therapeutic value only being considered.

The more significant changes in the U.S.P. XII are summarized in the following tables. The page numbers refer to pages in the text on which the preparations are discussed. Observe the new official names of certain drugs and preparations, particularly, diphenylhydantoin (dilantin), butacaine (butyn), butyl aminobenzoate (butesin), chloroazodin (azochloramid), menadione (2-methyl-1, 4-naphthoquinone), mercurophylline (mercupurin), neostigmine (prostigmine), pamaquine (plasmochin), quinacrine (atabrine), solution of tribromethanol (avertin with amylene hydrate), sulfobromophthalein (bromsulphalein).

TABLE I

ARTICLES ADDED TO THE U. S. P. XII *

DRUG	TEXT PAGE
Aluminum Hydroxide Gel (Colloidal Aluminum Hydroxide)	788
Aminoacetic Acid (Glycocoll, Glycine)	386
Amylene Hydrate (Tertiary Amyl Alcohol)	100
Butacaine Sulfate	298
Butyl Aminobenzoate	303
Calcium Mandelate	841
Carbarsone	937
Chloroazodin	848
Dihydromorphinone Hydrochloride	207
Diphenylhydantoin Sodium	165
Dried Aluminum Hydroxide Gel	788
Elixir Phenobarbital	140
Epinephrine Hydrochloride Spray (Solution of Epinephrine Hydrochloride 1:100)	411
Ergonovine Maleate	661
Ergotamine Tartrate	483, 661
Estradiol Benzoate	1198
Estrone (Theelin)	1198
Ethyl Carbamate (Urethane)	182
Eucatropine Hydrochloride	480
Exsiccated Ferrous Sulfate	1111
Halibut Liver Oil	1276, 1284
Hexylresorcinol	892
Magnesium Trisilicate	786
Menadione (2-Methyl-Naphthoquinone)	1295
Mercurophylline Injection	641
Mersalyl	640
Mersalyl and Theophylline Injection	641
Neostigmine Bromide	382
Neostigmine Methylsulfate	382
Nicotinamide (Nicotinic Acid Amide, Niacinamide)	1257
Ouabain (G-Strophanthin)	525
Pamaquine Naphthoate (Aminoquin Naphthoate)	916
Picrotoxin (Cocculin)	264
Potassium Chloride	598
Quinacrine Hydrochloride (Mepacrine Hydrochloride)	918
Quinine Hydrochloride	912
Riboflavin (Lactoflavin)	1253
Solution of Tribromoethanol	100
Sulfapyridine	1068
Sulfarsphenamine	952
Sulfathiazole	1089
Sulfobromophthalein Sodium	866
Sterile Sulfapyridine Sodium	1068
Syrup of Glycyrrhiza (Syrup of Licorice)	1318
Tetrachloroethylene	891
Theobromine and Sodium Acetate	281, 637
Trichloroethylene	76
Urea (Carbamide)	632

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* Official synonyms appear in parentheses.

TABLE II

ARTICLES OFFICIAL IN THE U. S. P. XI BUT NOT ADMITTED TO THE U. S. P. XII

DRUG	TEXT PAGE
Acetyltannic Acid	773
* Aconite	574
* Acriflavine	864
* Acriflavine Hydrochloride	864
Albumin Tannate	774
* Ammonium Bromide	162
* Ammonium Salicylate	230
* Bismuth Subgallate	768
Calcium Bromide	162
* Calcium Creosotate	819
Cannabis	183
* Cantharides	771
* Cantharides Cerate	771
* Cantharides Plaster	771
* Carbromal	127
* Chlorinated Paraffin	848
* Cinchona	913
* Compound Mixture of Opium and Glycyrrhiza	205
* Compound Tincture of Cinchona	913
* Copaiba	874
Corn Oil	768
* Creosote	818
* Creosote Carbonate	819
* Dichloramine-T	848
* Diluted Acetic Acid	839
* Diluted Solution of Sodium Hypochlorite	847
* Elixir of Glycyrrhiza	1321
* Ethylhydrocupreine Hydrochloride	915
Extract of Cannabis	184
* Extract of Nux Vomica	262
* Fluidextract of Belladonna Root	472
Fluidextract of Cannabis	184
* Guaiacol	818
* Iodoform	845
Merbaphen	640
* Oil of Santal	874
* Paraffin	768
* Pepsin	792
* Podophyllum	801
* Potassium Chlorate	852
* Powder of Ipecac and Opium	205
* Pyrogallol	833
* Quinine	912
* Resin of Podophyllum	801
* Santonin	884
* Sodium Acetate	624
* Solution of Ammonium Acetate	816
* Solution of Ferric Chloride	1116
* Spirit of Ethyl Nitrite	560
* Squill	525
* Strychnine Nitrate	262
* Sulfonethylmethane	182
* Syrup of Squill	525
* Theobromine with Sodium Salicylate	281, 637
* Tincture of Aconite	574
* Tincture of Ferric Chloride	1117
* Tincture of Squill	525
* Tincture of Veratrum Viride	575
* Veratrum Viride	575
* Washed Sulfur	871
* Yellow Mercurous Iodide	987

* Articles now official in the National Formulary, Seventh edition (November 1, 1942).

TABLE III

CHANGES IN OFFICIAL TITLES

U.S.P.XI	U.S.P.XII
Caffeine with Sodium Benzoate	Caffeine and Sodium Benzoate
Chiniofon Powder	Chiniofon
Compound Solution of Iodine	Strong Solution of Iodine
Diluted Erythrityl Tetranitrate	Erythrityl Tetranitrate Tablets
Glucose	Liquid Glucose
Nitrogen Monoxide	Nitrous Oxide
Purified Solution of Liver	Liver Injection
Soluble Barbital	Barbital Sodium
Soluble Fluorescein	Fluorescein Sodium
Soluble Iodophthalein	Iodophthalein Sodium
Soluble Pentobarbital	Pentobarbital Sodium
Soluble Phenobarbital	Phenobarbital Sodium
* Solution of Epinephrine Hydrochloride	Solution of Epinephrine Hydrochloride Epinephrine Hydrochloride Injection
Solution of Histamine Phosphate	Histamine Phosphate Injection
Solution of Parathyroid	Parathyroid Injection
Solution of Posterior Pituitary	Posterior Pituitary Injection
Stomach	Powdered Stomach
Theophylline with Ethylene Diamine	Theophylline Ethylenediamine
Theophylline with Sodium Acetate	Theophylline and Sodium Acetate
Volatile Oil of Mustard	Allyl Isothiocyanate

* Formerly used for oral as well as intravenous purposes. A non-sterile solution under this title is now retained for oral use, while a sterile solution is recognized under the title Epinephrine Hydrochloride Injection.

The U.S.P. XII has made official a number of convenient pharmaceutical preparations, such as capsules, tablets, and sterile solutions of drugs in ampules for parenteral administration ("Injections"). The more important articles in each of these categories are as follows:

Capsules (Example, *Digitalis Capsules*): Ammonium Chloride, Carbon Tetrachloride, Concentrated Oleovitamin A and D, Digitalis, Diphenylhydantoin Sodium, Halibut Liver Oil, Iron and Ammonium Citrates, Oil of Chenopodium, Oleovitamin A, Pentobarbital Sodium, Tetrachloroethylene, Theobromine and Sodium Acetate.

Tablets (Example, *Digitalis Tablets*): Acetophenetidin, Acetylsalicylic Acid, Ascorbic Acid, Atropine Sulfate, Barbital, Barbital Sodium, Cascara Sagrada, Chiniofon, Codeine Phosphate, Codeine Sulfate, Colchicine, Digitalis, Dihydromorphinone Hydrochloride, Ephedrine Sulfate, Ergonovine Maleate, Ergotamine Tartrate, Extract of Ox Bile, Ferrous Sulfate, Magnesium Trisilicate, Menadione, Methenamine, Morphine Sulfate, Neocinchophen, Neostigmine Bromide, Nicotinamide, Nicotinic Acid, Pentobarbital, Phenobarbital, Phenobarbital Sodium, Potassium Chloride, Quinacrine Hydrochloride, Quinidine Sulfate, Quinine Sulfate, Riboflavin, Saccharin Sodium, Sodium Nitrite, Sodium Salicylate, Strychnine Sulfate, Sulfanilamide, Sulfapyridine, Sulfathiazole, Theophylline, Theophylline Ethylenediamine, Theophylline and Sodium Acetate, Thiamine Hydrochloride, Thyroid, Tribasic Magnesium Phosphate.

Injections (Example, *Digitalis Injection*): Bismuth and Potassium Tartrate, Bismuth Subsalicylate, Caffeine and Sodium Benzoate, Calcium Gluconate, Dextrose, Dextrose and Sodium Chloride, Digitalis, Emetine Hydrochloride, Epinephrine Hydrochloride, Mercuric Salicylate, Mercurophylline, Mersalyl and Theophylline, Neostigmine Methylsulfate, Ouabain, Phenolsulfonphthalein, Picrotoxin, Quinine Hydrochloride and Ethyl Carbamate, Strophanthin, Sulfobromophthalein Sodium, Theophylline Ethylenediamine.

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